The Flavor and Fragrance High Production Volume Consortia (FFHPVC)

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December 27, 2000

Carol Browner, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Browner:

On behalf or the member companies of the Aromatic Consortium, the Flavor and Fragrance High Production Volume Consortia is pleased to submit the Test Plan and Robust Summaries for the chemical category designated the "Cinnamyl Derivatives" to the HPV Challenge Program, AR-201. The Aromatic Consortium has chosen not to belong to the HPV Tracker System for submission of test plans and robust summaries. We are therefore submitting the test plan and accompanying robust summaries directly to EPA to make available to the public.

This submission includes one electronic copy in pdf. format and one hard copy. The EPA registration number for the Aromatic Consortium is 1101122.

Please feel free to contact me with any questions or comments you might have concerning the submission (tadams@therobertsgroup.net) or 202-331-2325).

Sincerely,

Timothy Adams, Ph.D.
Technical Contact Person for FFHPVC

The Flavor and Fragrance High Production Volume Consortia

The Aromatic Consortium

Test Plan for Cinnamyl Derivatives

Cinnamaldehyde (3-phenyl-2-propenal)	**CAS No. 104-55-2**
***alpha*-Amylcinnamaldehyde (2-amyl-3-phenyl-2-propenal)**	**CAS No. 122-40-7**
***alpha*-Hexylcinnamaldehyde (2-hexyl-3-phenyl-2-propenal)**	**CAS No. 101-86-0**
***p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde (3-(*p*-t-butylphenyl)-2-methylpropanal)**	**CAS No. 80-54-6**

FFHPVC Aromatic Consortium Registration Number 1101122

Submitted to the EPA under the HPV Challenge Program by:

The Flavor and Fragrance High Production Volume Chemical Consortia

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List of Member Companies

BASF

BF Goodrich Company

Bush Boake Allen, Incorporated

Eastman Chemical

Firmenich, Incorporated

Givaudan Corporation

Haarmann & Reimer

ICI Americas

International Flavor & Fragrances, Inc.

KoSa

Polarome

Rhodia, Incorporated

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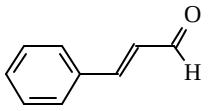
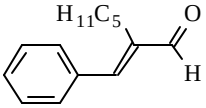


Cinnamaldehyde

3-phenyl-2-propenal

CAS No. 104-55-2



***alpha*-Amylcinnamaldehyde**

2-amyl-3-phenyl-2-propenal

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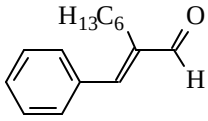

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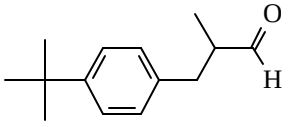


***p*-t-Butyl-*alpha*-methylhydrocinnamaldehyde**

3-(*p*-t-butylphenyl)-2-methylpropanal

CAS No. 80-54-6

2 Category Analysis

2.1 Introduction

In October of 1999, members of the U.S. flavor and fragrance industries and other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia are committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The Aromatic Consortium, as a member of the FFHPVC serves as an industry consortium to coordinate testing activities for aromatic substances under the Chemical Right-to-Know Program. Twelve (12) companies are current members of the Aromatic Consortium. The Aromatic Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and, where needed, conducting additional testing. The test plan, category analysis and robust summaries presented below are the first phase of the Aromatic Consortium's commitment to the Chemical Right-to-Know Program.

2.2 Background Information

The chemical category designated "Cinnamyl Derivatives" includes cinnamaldehyde, two alkyl-substituted cinnamaldehydes, and one alkyl-substituted dihydrocinnamaldehyde derivative. The four substances are grouped together because of their close structural relationships and the resulting similarities of their physio-chemical and toxicological properties.

In nature, cinnamaldehyde is the predominant constituent of cassia oil and Ceylon cinnamon bark oil. It is responsible for the spicy aroma strongly reminiscent of cinnamon spice. It is common components of traditional foods. Cinnamaldehyde, *alpha*-amylcinnamaldehyde, and *alpha*-hexylcinnamaldehyde are currently recognized by the U.S. Food and Drug Administration (FDA) as GRAS ("generally regarded as safe") for their intended use as flavoring substances [Hall and Oser, 1965]. *p*-t-Butyl-*alpha*-

methylhydrocinnamaldehyde is used only in fragrance products. Quantitative natural occurrence data for cinnamaldehyde indicates that oral intake occurs predominantly from consumption of cinnamon spice products and cinnamon flavorings [Stofberg and Grundschober, 1987; Stofberg and Kirschman, 1985]. Greater than 38,000 kg [Stofberg and Grundschober, 1987] of cinnamaldehyde is consumed annually as a natural component of food while 451,400 kg is consumed as an added flavoring substance in the U.S.A. annually [Lucas *et al.*, 1999].

alpha-Amylcinnamaldehyde and *alpha*-hexylcinnamaldehyde have a flowery aroma reminiscent of jasmine and are widely used as fragrance ingredients in cosmetics, soaps, detergents and other fragranced consumer products. Because both substances are stable in alkali, they are used in soap perfumes. *p*-t-Butyl-*alpha*-methylhydrocinnamaldehyde, commonly recognized as lilial, produces a stable and long lasting pleasant, mild blossom odor popular in soap and cosmetic products with a "lily of the valley" or linden fragrance.

2.3 Structural Classification

The four substances in this group are un-substituted or alkyl-substituted cinnamaldehyde or 2,3-dihydrocinnamaldehyde derivatives. Common structural features among members of this chemical category are that they contain either a 3-phenyl-2-propenal or 3-phenylpropanal backbone. The group includes cinnamaldehyde (3-phenyl-2-propenal), *alpha*-amylcinnamaldehyde (2-amyl-3-phenyl-2-propenal), *alpha*-hexylcinnamaldehyde (2-hexyl-3-phenyl-2-propenal) and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde {3-(*p*-t-butylphenyl)-2-methylpropanal}.

2.4 Production of Cinnamyl Derivatives

The *trans*- isomer of cinnamaldehyde predominates in nature. On a commercial scale, cinnamaldehyde is prepared almost exclusively from the alkaline condensation of benzaldehyde and acetaldehyde [Richmond, 1950]. In a similar manner, *alpha*-amylcinnamaldehyde and, *alpha*-hexylcinnamaldehyde are prepared by the condensation of heptanal and octanal, respectively, with benzaldehyde. These aldehydes must be protected from oxidation to the corresponding carboxylic acid. Therefore, antioxidants

are added as stabilizers. The remaining substance in the chemical category, *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde is prepared by the condensation of *p*-t-butylbenzaldehyde with propanal. It is also prepared by reduction of *alpha*-methylcinnamaldehyde to yield *alpha*-methylhydrocinnamic alcohol. The alcohol is then alkylated with *tert*-butyl chloride and subsequently oxidized to the aldehyde [Webb, 1981].

2.5 Chemical Reactivity and Metabolism

2.5.1 Absorption, Distribution, and Excretion

Cinnamaldehyde, the *alpha*-amyl and *alpha*-hexyl derivatives and its saturated analog (*p*-t-butyl-*alpha*-methyldihydrocinnamaldehyde) are rapidly absorbed from the gut, metabolized and excreted primarily in the urine and, to a minor extent, in the feces. Rodent and humans studies for cinnamaldehyde and *alpha*-substituted cinnamaldehydes indicate that cinnamyl derivatives are absorbed, metabolized and excreted as polar metabolites within 24 hours.

The tissue distribution and excretion of cinnamaldehyde has been studied in male F344 rats [Sapienza *et al.*, 1993]. Groups of male rats (8/group) were pretreated with single daily oral dose levels of 5, 50, or 500 mg/kg bw of cinnamaldehyde by gavage for seven days. Twenty-four (24) hours later, animals in each group received a single oral dose of [3-^{14}C]-cinnamaldehyde equivalent to the pretreatment level. Groups of rats (8/group) receiving no pretreatment were also given single oral doses of 5, 50 or 500 mg/kg bw. Radioactivity was distributed primarily to the gastrointestinal tract, kidneys, and liver, after single oral dose and multiple oral administrations. After 24 hours, more than 80% of the radioactivity was recovered in the urine and less than 7% in the feces from all groups of rats, regardless of dose level. At all dose levels, a small amount of the dose was distributed to the fat. At 50 and 500 mg/kg bw, radioactivity could be measured in animals terminated 3 days after dosing. Except for the high dose pretreatment group, the major urinary metabolite was hippuric acid, accompanied by small amounts of cinnamic and benzoic acid. In the high dose pretreatment group, benzoic acid was the major

metabolite, suggesting that saturation of the glycine conjugation pathway occurs at repeated high dose levels of cinnamaldehyde.

The effect of dose and sex on the disposition of [3-^{14}C]-cinnamaldehyde has been studied in F344 rats or CD1 mice [Peters and Caldwell, 1994]. Greater than 85% of either a 2.0 or 250 mg/kg bw dose of cinnamaldehyde administered to groups of male and female F344 rats (4/group) or CD1 mice (6/group) by intraperitoneal injection was recovered in the urine and feces within 24 hours. Greater than 90% was recovered after 72 hours. When 250 mg/kg bw of [3-^{14}C]-cinnamaldehyde was administered orally to F344 rats, 98% was recovered from the urine (91%) and feces (7%) within 24 hours [Peters and Caldwell, 1994]. The effect of dose on the disposition of [3-^{14}C-d_5]-cinnamic acid in F344 rats and CD1 mice has also been studied. Five dose levels of cinnamic acid in the range from 0.0005 mmol/kg bw (0.072 mg/kg bw) to 2.5 mmol/kg bw (370 mg/kg bw) were given orally to groups of F344 rats (4/group) or by intraperitoneal injection to groups of CD1 mice (4/group). After twenty-four (24) hours, 73-88% of the radioactivity was recovered in the urine of rats and 78-93% in the urine of mice. After 72 hours, 85-100% of the radioactivity was recovered from rats mainly in the urine [Caldwell and Nutley, 1986]. In mice, the recovery was 89-100% within 72 hours. Only trace amounts of radioactivity were present in the carcasses, indicating that cinnamic acid was readily and quantitatively excreted at all dose levels [Nutley *et al.*, 1994]. In summary, it appears that the parent alcohol, aldehyde, and acid undergo rapid absorption, metabolism, and excretion independent of dose (up to 250 mg/kg bw), species, sex, and mode of administration.

In rats, *alpha*-methylcinnamaldehyde [Kay and Raper, 1924] and *p*-methylcinnamic acid [Solheim and Scheline, 1973] are rapidly absorbed, metabolized, and excreted in the urine as free and conjugated forms of cinnamic acid or benzoic acid. Based on these studies, cinnamyl derivatives are anticipated to be rapidly absorbed, metabolized, and excreted mainly in the urine within 24 hours.

2.5.2 Oxidation and Conjugation Reactions

The aromatic cinnamaldehyde derivatives are readily oxidized to cinnamic acid derivatives (see Figure 1). Human NAD^+ dependent alcohol dehydrogenase (ADH) catalyzes oxidation of primary alcohols to aldehydes [Pietruszko *et al.*, 1973]. Isoenzyme mixtures of NAD^+ dependent aldehyde dehydrogenase (ALD) [Weiner, 1980] catalyze oxidation of aldehydes to carboxylic acids. Aromatic alcohols and aldehydes have been reported to be excellent substrates for ADH [Sund and Theoell, 1963] and ALD [Feldman and Wiener, 1972], respectively. The urinary metabolites of cinnamyl alcohol and cinnamaldehyde are mainly derived from metabolism of cinnamic acid (see Figure 1).

Doses of 2 and 250 mg trans-[3-^{14}C]cinnamaldehyde/kg bw were given by ip. injection to male and female Fischer 344 rats and CD1 mice [Peters and Caldwell, 1994]. Doses of 250 mg/kg bw were also administered via oral gavage to male rats and mice only. In both species, the major urinary metabolites were formed from oxidation of cinnamaldehyde to yield cinnamic acid, which was subsequently oxidized in the *beta*-oxidation pathway. The major urinary metabolite was hippuric acid (71-75% in mice and 73-87% in rats), accompanied by small amounts of metabolites including 3-hydroxy-3-phenylpropionic acid (0.4-4%), benzoic acid (0.4-3%), and benzyl glucuronide (0.8-7.0%). The glycine conjugate of cinnamic acid was formed to a considerable extent only in the mouse (4-13%). To a small extent, glutathione conjugation of cinnamaldehyde competes with the oxidation pathway. Approximately 6-9% of either dose was excreted in 24 hours as glutathione conjugates of cinnamaldehyde. The authors concluded that the excretion pattern and metabolic profile of cinnamaldehyde in rats and mice are not systematically affected by sex, dose size, or route of administration [Peters and Caldwell, 1994].

The toxicokinetic profile of cinnamaldehyde has been investigated in male F344 rats [Yuan and Deiter, 1992]. Plasma levels of cinnamaldehyde (less than 0.1 μg/ml) and cinnamic acid (less than 1 μg/ml) were not measurable when rats (3-6/group) were administered a single oral dose of 50 mg/kg bw of cinnamaldehyde by gavage in corn oil. At dose levels of 250 and 500 mg/kg bw, plasma levels of cinnamaldehyde and cinnamic acid were ≈1 and less than 10 μg/ml, respectively. The bioavailability of cinnamaldehyde was calculated to be less than 20% at both dose levels. A dose-dependent increase in

hippuric acid, the major urinary metabolite, occurred 6 hours after gavage and continued over the next 18 hours. Only small amounts of cinnamic acid were excreted in the urine either free or as the glucuronic acid conjugate. The urinary hippuric acid recovered over 50 hours accounted for 72-81% over the dose range from 50 to 500 mg/kg bw.

Approximately 15% of an oral dose of 250 mg cinnamaldehyde/kg bw administered to rats by gavage was excreted in the urine as two mercapturic acid derivatives, N-acetyl-S-(1-phenyl-3-hydroxypropyl)cysteine and N-acetyl-S-(1-phenyl-2-carboxyethyl)cysteine, in a ratio of four to one. Approximately 9% of an oral dose of 125 mg cinnamyl alcohol/kg bw was excreted in the urine as N-acetyl-S-(1-phenyl-3-hydroxypropyl)cysteine [Delbressine *et al.*, 1981].

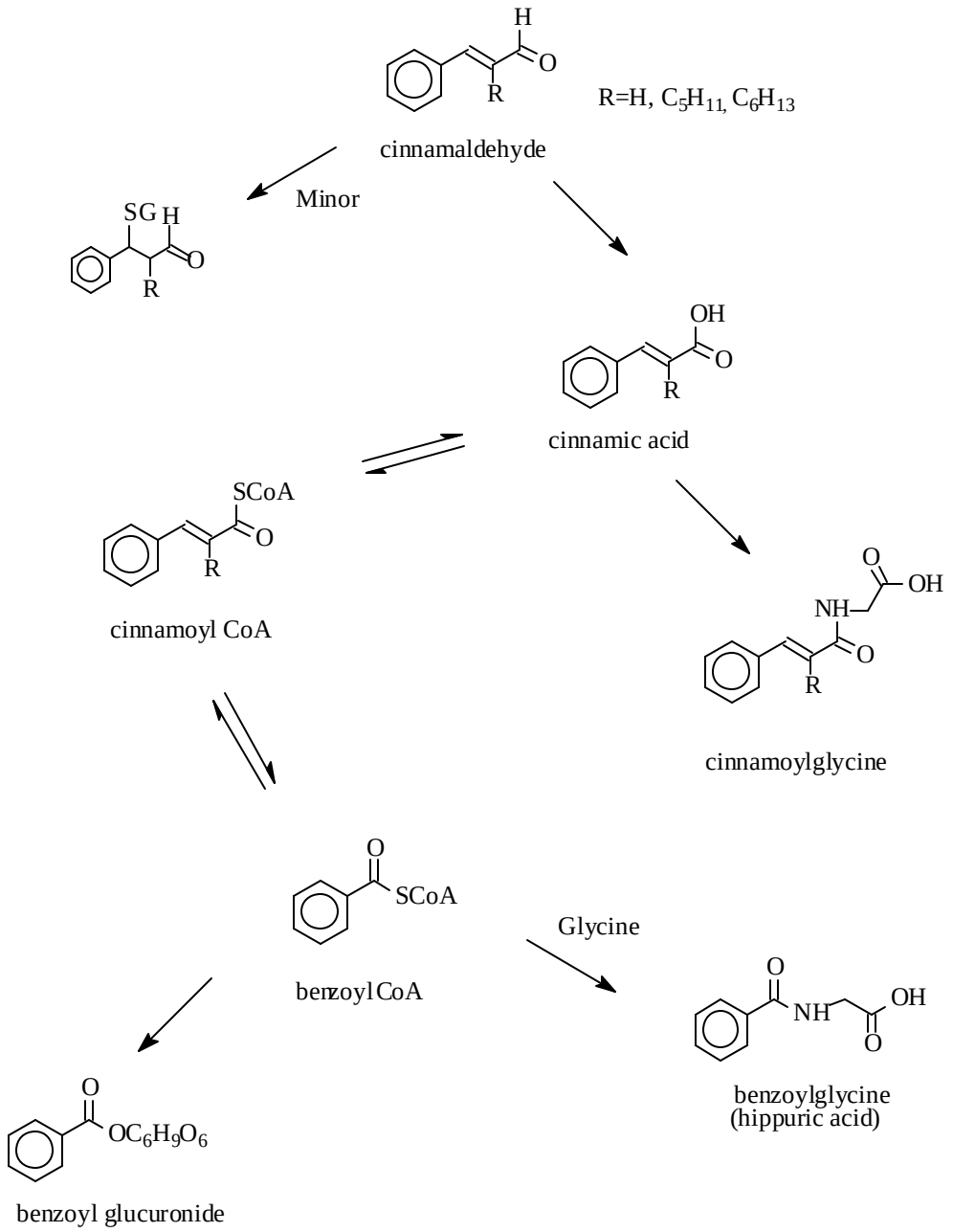
The position and size of the substituent do not significantly affect the pathways of metabolic detoxication of cinnamyl derivatives. Cinnamyl derivatives containing *alpha*-alkyl substituents (e.g. *alpha*-methylcinnamaldehyde) are extensively metabolized *via* *beta*-oxidation followed by cleavage to yield mainly the corresponding hippuric acid derivative. A benzoic acid metabolite was isolated from the urine of dogs given either *alpha*-methylcinnamic acid or *alpha*-methylphenylpropionic acid [Kay and Raper, 1924]. These studies suggest that *alpha*-methylcinnamaldehyde undergoes oxidation to benzoic acid while higher homologues are excreted primarily unchanged or as the conjugated form of the cinnamic acid derivative.

para (*p*-) Ring substituents (e.g. 3-(*p*-isopropylphenyl)propionaldehyde and *p*-methylcinnamaldehyde) do not significantly impact metabolism via *beta*-oxidation. In male albino rats, *p*-methoxycinnamic acid has been shown to be metabolized primarily to *p*-methoxybenzoic acid and its corresponding glycine conjugate [Solheim and Scheline, 1973]. Similar results were reported with 3,4-dimethoxycinnamic acid (which is meta and para substituted) [Solheim and Scheline, 1976]. The structurally related substance *p*-tolualdehyde is metabolized to *p*-methylbenzoic acid without any apparent oxidation of the methyl group [Williams, 1959]. Based on these observations, it may be concluded that the presence of side-chain alkyl substituents and ring substituents do not alter the principal metabolic detoxication pathway for cinnamyl derivatives. Each of the four

cinnamyl derivatives is oxidized to the corresponding acid followed either by conjugation and excretion or by *beta*-oxidation, conjugation and excretion.

Figure 1

Metabolism of Cinnamaldehyde Derivatives



3 Test Plan

3.1 Chemical and Physical Properties

3.1.1 Melting Point

The melting point of cinnamaldehyde is reported to be -7.5^{o}C [Merck, 1997] while that of *alpha*-hexylcinnamaldehyde is 4^{o}C [Fenaroli's, 1994]. The calculated [SRC] melting points (0.04 to 46^{o}C) are significantly higher than experimental values.

3.1.2 Boiling Point

The increase in experimental boiling points in going from cinnamaldehyde (246^{o}C [Merck, 1997] and 250^{o}C [FMA]), *alpha*-amylcinnamaldehyde (284^{o}C [FMA]), *alpha*-hexylcinnamaldehyde (304^{o}C [FMA]), to *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde (258^{o}C [Arctander, 1969]) is consistent with an increase in molecular weight and alkyl group branching. Boiling points calculated by the Stein and Brown Method produce the same trend in boiling points for cinnamaldehyde (227^{o}C), *alpha*-amylcinnamaldehyde (305^{o}C), *alpha*-hexylcinnamaldehyde (319^{o}C), and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde (280^{o}C) but the difference in boiling point between cinnamaldehyde and the three alkyl-substituted cinnamaldehyde derivatives is greater than experimentally determined values.

3.1.3 Vapor Pressure

The reported vapor pressure for *alpha*-hexylcinnamaldehyde, 0.0002 mm Hg [Vuilleumier, 1995] is in good agreement with calculated vapor pressures of less than 0.001 [FMA] and 0.00048 mm Hg (Modified Grain Method) [SRC]. The calculated vapor pressure of less than 0.001 mm Hg [FMA] and 0.0012 mm Hg (Modified Grain Method) [SRC] for *alpha*-amylcinnamaldehyde, and 0.00358 mm Hg (Modified Grain Method) for *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde [SRC] are consistent with that of *alpha*-hexylcinnamaldehyde (, since their increased vapor pressure reflect their decreased molecular weights (14 daltons less than the *alpha*-hexyl derivative). Cinnamaldehyde, having the lowest molecular weight, exhibits a proportionately higher

calculated vapor pressure of 0.02 mm Hg [FMA] and 0.09 mm Hg (Antoine and Grain Method) [SRC].

3.1.4 Octanol/Water Partition Coefficients

The calculated log Kow values [SRC] of 4.33 for *alpha*-amylcinnamaldehyde, 4.82 for *alpha*-hexylcinnamaldehyde, and 4.36 for *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde follow the same trend but are slightly lower than experimental values of 4.7 [Givaudan-Roure, 1994a], 5.3 [Givaudan-Roure, 1994d], and 4.2 [Givaudan-Roure, 1994b], respectively determined by OECD guideline 117. Experimental values show a slightly higher lipophilic character (*i.e.*, higher log Kow) than are estimated by the model [SRC]. The experimental log Kow for the more polar, lower molecular weight aldehyde, cinnamaldehyde, is also expected to be slightly lower than the calculated log Kow of 1.82 [SRC].

3.1.5 Water Solubility

The water solubilities of 33 mg/L [Givaudan-Roure, 1995] obtained according to OECD 105 guideline and less than 100 mg/L [Givaudan-Roure, 1994b] and 200 mg/L [BBA, 1990] reported using other experimental procedures for *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde are an order of magnitude greater than the calculated solubility of 7.8 mg/L (KOWWIW). Other calculated solubilities of 8.5 mg/L for *alpha*-amylcinnamaldehyde, 2.75 mg/L for *alpha*-hexylcinnamaldehyde, and 2150 mg/L for cinnamaldehyde are expected to be 5-10 times less than experimentally measured water solubilities. Because of the wide discrepancies between measured and calculated values for water solubility, it is recommended that water solubilities be measured using OECD guidelines for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

3.1.6 New Testing Required

Measurement of water solubility is recommended for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

3.2 Environmental Fate and Pathways

3.2.1 Photodegradation

The calculated photodegradation half lives (AOPWIN) of the four cinnamaldehyde derivatives are in the range from 2.33 to 3.88 hrs. Structurally, 3 of the 4 substances in this category are *alpha,beta*-unsaturated aldehydes. These substances have an oxidizable aldehyde function and an allylic position (C_4) labile to attack by hydroxy radical species in the gas phase. The known chemical reactivity of these substrates supports short photodegradation half-lives predicted by the model.

3.2.2 Stability in Water

No hydrolysis is possible for any of these 4 cinnamaldehyde derivatives. All four are expected to be relatively stable in aqueous solution, although they may be slowly oxidized to the corresponding cinnamic acid derivative in aqueous media.

3.2.3 Biodegradation

Studies for *alpha*-amylcinnamaldehyde, *alpha*-hexylcinnamaldehyde, and *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde demonstrate these materials to be readily biodegradable. Biodegradation of *alpha*-amylcinnamaldehyde was 70.5% and 90% after 28 days using OECD test guidelines 301B [Quest, 1996] and 301F [Givaudan-Roure, 1992a], respectively. Similarly, *alpha*-hexylcinnamaldehyde was 76.5% and 97% biodegraded after 28 days using OECD test guidelines 301B [Quest, 1994] and 301F [Givaudan-Roure, 1992b], respectively and *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde was 84% and 96% biodegraded after 28 days using test OECD guideline 301F [Givaudan-Roure, 1994c; BBA, 1990]. The three cinnamyl derivatives met the 10 day window criteria for biodegradability. Although no biodegradation study is available for cinnamaldehyde, this substance, like the other three cinnamaldehyde derivatives contains an oxidizable aldehyde function. There is no reason to suspect that cinnamaldehyde will not be readily biodegradable using either test OECD guideline 301B or 301F.

3.2.4 Fugacity

Transport and distribution in the environmental were modeled using Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11 [Mackay and Donald, 1991]. The principal input parameters into the model are molecular weight, melting point, vapor pressure, water solubility, and log Kow. Where measured values were available, these were used but where they were not, calculated data from the EPIWIN series of programs were used. Based on the comparable physiochemical properties of the four aldehydes, it is not unexpected that the four would exhibit similar distribution in the environment. The significance of these calculations must be evaluated in the context that the substances in this chemical category are readily oxidized in the environment to corresponding carboxylic acids. The aldehydes have been shown to be readily and/or ultimately biodegradable, and the remainder would be expected to behave similarly in the environment. Since the model does not account the effects of biodegradation, the relevance of fugacity calculations for these substances is highly questionable.

3.2.5 New Testing Required

None

3.3 Ecotoxicity

3.3.1 Acute Toxicity to Fish

Only ECOSAR calculated values are available. The 96-hour LC50 for cinnamaldehyde is calculated to be 11.9 mg/L while the alkyl substituted homologues *alpha*-amylcinnamaldehyde and *alpha*-hexylcinnamaldehyde, being more lipophilic, are calculated to have LC50 values about one third of that for cinnamaldehyde (3.14 mg/L and 2.36 mg/L, respectively). The remaining substance *p-t-butyl-alpha-methylhydrocinnamaldehyde* possessing the same molecular weight as *alpha*-amylcinnamaldehyde and is also an alkyl substituted cinnamaldehyde is calculated to have approximately the same LC50 (LD50=3.19 mg/L). Because of the lack of fish acute toxicity data on this group, the QSAR algorithm should be validated by conducting LC50 assays with cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

3.3.2 Acute Toxicity to Aquatic Invertebrates

Only an ECOSAR calculated value is available for cinnamaldehyde at 8.1 mg/L (48-hour Daphnia LC50). It does not differ significantly from that for fish. The Daphnia 48-hour LC50s for the more lipophilic substances *alpha*-amylcinnamaldehyde and *alpha*-hexylcinnamaldehyde are calculated to be 0.416 and 0.224 mg/L, respectively. The calculated LC50 for *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde is in the same range, 0.403 mg/L. Because of the lack of data on this chemical category, the QSAR algorithm should be validated by conducting tests on cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

3.3.3 Acute Toxicity to Aquatic Plants

The only study of algae toxicity indicates that a 50 uM solution of cinnamaldehyde inhibits the growth of green algae by 35% after 80 hours and 5% after 160 hours [Dedonder, 1971]. ECOSAR calculated 48-hour EC50 values for cinnamaldehyde (8.1 mg/L), *alpha*-amylcinnamaldehyde (0.871 mg/L), *alpha*-hexylcinnamaldehyde (0.343 mg/L), and *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde (0.827 mg/L) are consistent with calculated values for acute fish and aquatic invertebrate toxicity cited above. The QSAR algorithm should be validated by conducting tests on cinnamaldehyde and *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde because of the lack of data on this group. Assuming the measured values for cinnamaldehyde and *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyde in fish, Daphnia, and green algae are greater than calculated values; it will not be necessary to conduct this test on the other two members of this chemical category.

3.3.4 New Testing Required

- Acute toxicity to fish by OECD guideline 203 for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamic aldehyde. (Due to limited solubility of these substances, LC50 will be carried out only up to the solubility limit of the substance in a static-renewal test.)

- Acute toxicity to Daphnia by OECD guideline 202 for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

- Acute toxicity to algae according to OECD guideline 201 for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde.

3.4 Human Health Data

3.4.1 Acute Toxicity

Oral LD50 values have been reported for the four substances in this chemical category. In rats, LD50 values are in the range of 2220-3400 mg/kg, demonstrating that the oral acute toxicity of these substances is extremely low [Denine and Palanker, 1973; Jenner *et al*., 1964; Keating, 1972; Levenstein and Wolven, 1972; Levenstein, 1975; Levenstein, 1976; Moreno, 1971; Moreno, 1972; Moreno, 1973; Moreno, 1974; Moreno, 1975; Moreno, 1976; Moreno, 1977a; Moreno, 1981; Moreno, 1982; Opdyke, 1974; Russell, 1973; Schafer *et al.*, 1983; Weir and Wong, 1971; Wohl, 1974; Zaitsev and Rakhmanina, 1974]. Lowest LD50 values are reported for cinnamaldehyde (LD50=1160 mg/kg) while LD50 values for the alkyl-substituted derivatives are in the range from 3100 mg/kg to 3730 mg/kg. LD50 values in the range from approximately 2318 to 3400 mg/kg have been reported in mice [Draize *et al*., 1948; Harada and Ozaki, 1972; Levenstein, 1975; Schafer and Bowles, 1985; Zaitsev and Rakhmanina, 1974].

Dermal acute toxicity shows a similar trend for the four substances in this chemical category. Dermal LD50 values range from a low of 590 ul/kg for cinnamaldehyde to more than 2000 mg/kg for *alpha*-amylcinnamaldehyde, more than 3000 mg/kg for *alpha*-hexylcinnamaldehyde, and more than 5000mg/kg for *p*-*t*-butyl-*alpha*-methylhydrocinnamaldehyd*e* [Moreno, 1971; Moreno, 1973b; Moreno, 1977b; Shelanski, 1973; Draize *et al.*, 1948; Zaitsev and Rakhmanina, 1974].

3.4.2 Genetic Toxicity

3.4.2.1 In vitro

Cinnamaldehyde (*trans* and unspecified stereochemistry), *alpha*-amylcinnamaldehyde, *alpha*-hexylcinnamaldehyde, and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde were inactive in *Salmonella typhimurium*, including strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, and TA2637. The assays were

performed at concentrations ranging up to the level of cytotoxicity, both in the absence and presence of metabolic activation (S9 fraction) obtained from the livers of Aroclor 1254 or methylcholanthrene-induced Sprague-Dawley rats or Syrian hamsters [Azizan and Blevins, 1995; Dillon *et al.*, 1992; Eder *et al.*, 1980; Eder *et al.*, 1982a; Eder *et al.*, 1982b; Eder *et al.*, 1991; Florin *et al.*, 1980; Fujita and Sasaki, 1987; Ishidate *et al.*, 1984; Kasamaki *et al.*, 1982; Lijinsky and Andrews, 1980; Marnett *et al.*, 1985; Neudecker *et al.*, 1983; Sekizawa and Shibamoto, 1982; Tennant *et al.*, 1987; Wild *et al.*, 1983; Wagner, 1999; Givaudan-Roure, 1984].

Some weakly equivocal-to-positive results were reported for cinnamaldehyde in *Salmonella typhimurium* strain TA100 using the pre-incubation method [Dillon *et al.*, 1992; Ishidate *et al.*, 1984]. However, the majority of similar studies in strain TA100, including a recent study using a prolonged pre-incubation time (120 minutes), and others using the standard plate incorporation method, did not find any evidence of mutagenicity [Azizan and Blevins, 1995; Eder *et al.*, 1982a, Eder *et al.*, 1982b; Eder *et al.*, 1991; Kasamaki *et al.*, 1982; Lijinsky and Andrews, 1980; Neudecker *et al.*, 1983; Sasaki and Endo, 1978; Sekizawa and Shibamoto, 1982; Wagner and Twarszik, 1999; Givaudan-Roure, 1984].

Mutation assays in *Escherichia coli* strains WP2 *uvrA* were negative for cinnamaldehyde and *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde [Yoo, 1986; Sekizawa and Shibamoto, 1982; Wagner, 1999]. Cinnamaldehyde produced equivocal to positive results in the forward mutation assay in L5178Y mouse lymphoma cells both with and without metabolic activation, but the reports describing these tests did not provide sufficient details on the methodology, test concentrations, or cytotoxic effects to adequately evaluate the results [Palmer, 1984; Rudd *et al.*, 1983]. In L1210 mouse lymphoma cells, DNA strand breaks were observed only at cytotoxic concentrations of cinnamaldehyde [Eder *et al.*, 1993].

Tests for the induction of sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells exposed to cinnamaldehyde produced negative results at low concentrations and weakly positive results at concentrations approaching cytotoxic levels, suggesting

only weak SCE activity [Galloway *et al.*, 1987; Sasaki *et al.*, 1987]. A dose-dependent increase in SCE was reported only when cultures were pre-treated with mitomycin C [Sasaki *et al.*, 1987]; however, in the absence of SCE activity by cinnamaldehyde alone, the activity in conjunction with mitomycin contributes little to the evaluation of the potential SCE activity. Cinnamaldehyde was reported to induce chromosome aberrations at low concentrations (*i.e.*, less than 15 ug/ml) in Chinese hamster fibroblasts and B241 cells tested with and without metabolic activation [Ishidate *et al.*, 1984; Kasamaki *et al.*, 1982; Kasamaki and Urasawa, 1985]. However, higher concentrations were negative in CHO cells, both with and without metabolic activation in a well-conducted, repeated assay [Galloway *et al.*, 1987]. Negative results were obtained with cinnamaldehyde in the mutation assay in Chinese hamster V79 cells [Fiorio and Bronzetti, 1994].

The positive results obtained in Mouse Lymphoma Assays (MLA) were at near-lethal concentrations in studies reporting cell lethality. The results of the MLA for simple aliphatic and aromatic substances have been shown to be inconsistent with the results of other standardized genotoxicity assays [Heck *et al.*, 1989; Tennant *et al.*, 1987]. Culture conditions of low pH and high osmolality, which may occur upon incubation with substances (aldehydes, carboxylic acids, and lactones) having a potentially acidifying influence on the culture medium, have been shown to produce false-positive results in this and other assays [Heck *et al.*, 1989].

3.4.2.2 In vivo

An increase in the frequency of sex-linked recessive lethal mutations (SRLM) was reported when *Drosophila melanogaster* was injected with 20,000 ppm cinnamaldehyde. However, no increase in the frequency of mutations occurred when *Drosophila melanogaster* were fed 800 ppm cinnamaldehyde for three days. Reciprocal translocations were not observed in either assay [Woodruff *et al.*, 1985]. The was no evidence of SLRM when *Drosophila melanogaster* were maintained on 10 mM solutions of either *alpha*-amylcinnamaldehyde or *alpha*-hexylcinnamaldehyde [Wild *et al.*, 1983].

In mammalian test systems, there was no evidence of an increase in unscheduled DNA synthesis in hepatocytes when rats or mice were administered 1000 mg

cinnamaldehyde/kg bw by oral gavage [Mirsalis *et al.*, 1989]. In the rodent micronucleus assay, the frequency of micronuclei was not increased when rats or mice were given 1700 mg/kg bw or 1100 mg/kg bw, respectively, of cinnamaldehyde by oral gavage [Mereto *et al*., 1994] or when mice were administered 500 mg/kg bw by intraperitoneal injection [Hayashi *et al.*1984, 1988]. The frequency of micronucleated bone marrow cells in mice that had been exposed to X-rays decreased after 500 mg cinnamaldehyde was administered by intraperitoneal injection [Sasaki *et al.*, 1990].

In one study [Mereto *et al.*, 1994], an increase in micronucleated cells was reported in rat and mouse hepatocytes, and in rat (but not in mouse) forestomach cells after oral gavage dosing with cinnamaldehyde up to 1,100 mg/kg/bw (rats) or 1,700 mg/kg/bw (mice). No increase in liver or forestomach micronuclei were observed at dose levels ≤ 850 mg/kg bw. No DNA fragmentation was observed in the rat hepatocytes or gastric mucosa cells. An increase in the incidence and size of GGT-positive foci was in reported hepatocytes of rats pretreated with *N*-nitrosodiethylamine and then administered 500 mg cinnamaldehyde/kg bw/day by oral gavage for 14 days [Mereto *et al.*, 1994].

The positive *in vivo* findings with cinnamaldehyde in the rat forestomach and in the liver of both rats and mice are inconsistent with negative results observed in the standard bone marrow assays and are observed at dose levels that result in significant toxicity. It has been reported that cinnamaldehyde given at oral doses of ≥ 500 mg/kg bw results in the depletion of hepatocellular glutathione levels [Swales and Caldwell, 1991; 1992; 1993]. Therefore, increases in micronuclei were reported at dose levels (1100 and 1700 mg/kg bw) that appear to affect cellular defense mechanisms (i.e., glutathione depletion). Based on the fact the micronuclei formation is dose-dependent; it appears that induction of micronuclei is a threshold phenomenon, which occurs at extremely high levels of intake. Also, the bolus doses resulting from gavage administration likely produce much greater exposures to both the forestomach and liver, as compared to dietary or dermal administration. The author [Mereto *et al.*, 1994] acknowledged these facts and concluded that the data did not justify the conclusion that cinnamaldehyde was clastogenic. As a result of the apparent threshold for micronuclei induction and the lack of activity in the remainder of the *in vivo* studies, the results obtained with bolus, high-dose exposures

occurring in the liver and forestomach are not considered relevant to the safety of cinnamaldehyde at normal exposure levels.

The conclusion that cinnamaldehyde and the three other cinnamyl derivatives are not mutagenic, is based on the results of three *in vivo* mouse micronucleus assays in which there was no evidence of an increase in the incidence of micronuclei when NMIR or ICR mice were given oral doses of 1213 mg/kg bw of *alpha*-amylcinnamyl alcohol [Wild *et al.*, 1983], 756 mg/kg bw of *alpha*-hexylcinnamaldehyde [Wild *et al.*, 1983], or 600 mg/kg of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde [Gudi and Krsmanovic, 2000].

3.4.2.3 Conclusion

Cinnamaldehyde and its alkyl-substituted derivatives lack direct mutagenic or genotoxic activity, as indicated by the negative results obtained in bacterial test systems. Evidence of genotoxic activity was observed in isolated mammalian cells, with the cinnamyl compounds producing chromosome aberrations and/or mutations in the respective test systems regardless of the presence or absence of metabolic activation; however, the reported *in vitro* activity did not translate into mutagenic, clastogenic, or genotoxic activity *in vivo.*

3.4.3 Repeat Dose Toxicity

Oral and/or dermal repeat-dose studies are available for each of the 4 substances in this chemical category.

Groups (10/sex/group) of male and female Osborne-Mendel rats were maintained on a diet containing either 0 (control), 1000, 2500, or 10,000 ppm (approximately equivalent to 50, 125, or 500 mg/kg bw/day, respectively) cinnamaldehyde for a total of 16 weeks. Measurement of body weight and food intake recorded weekly showed no significant difference between test and control animals at any dose level. At termination, hematological examinations revealed normal values. At necropsy, no differences were reported between major organ weights of test and control animals. Gross examination of the tissue of all animals was unremarkable. Histopathological examination of 6-8 animals, equally represented by gender, in the high-dose group revealed a slight hepatic

cellular swelling and a slight hyperkeratosis squamous epithelium of the stomach [Hagan *et al.*, 1967].

Groups of male and female rats (20/sex/group) were maintained on a diet containing cinnamaldehyde at levels calculated to result in the approximate daily intake of either 0 (control), 58, 114, or 227 mg/kg bw for 12 weeks. Observations of general condition and behavior, as well as measurements of bodyweight, food intake, and efficiency of food utilization were recorded regularly. No statistically significant differences between test and control animals were noted. At week 12 of experimentation, hematological examination revealed normal blood hemoglobin levels, and urinanalysis revealed the absence of urine glucose in either sex and only trace levels of albumin in male urines (attributed to the possible presence of semen). At necropsy, measurement of liver and kidney weights revealed no significant difference between test and control groups. Gross examination revealed occasional occurrence of respiratory infections in animals from all groups. Histopathological examination revealed no evidence of adverse effects that could be related to administration of the test substance [Trubeck Laboratories, 1958a].

In a 13-week study, groups of 10 male and 10 female F344/N rats were administered 0, 1.25, 2.5, 5.0, or 10.0% (0, 625, 1250, 2500, or 5000 mg/kg bw, respectively) microencapsulated cinnamaldehyde in the diet. Necropsies were performed on all survivors and histopathological examinations were performed on the two highest dose groups and the control group. There were no early deaths and no cinnamaldehyde-related clinical observations of toxicology. Group mean terminal body weight values were similar to untreated controls for the male and the female vehicle control group. However, the group mean body weight values decreased for males and females in the 2.5, 5.0, and 10.0% dose groups. Food consumption for treated male and female rats was depressed during the first study week and was attributed to taste aversion. Hematological evaluations did not show any overt cinnamaldehyde-related toxicity. Clinical chemistry parameters that were increased by treatment included bile salts and alanine transaminase levels (male and female 10.0% dose group), suggesting mild cholestasis. There were no morphological alterations to the liver based on microscopic examination. Gross necropsy findings were limited to the stomach of the 2.5, 5.0, and 10.0% dose groups [NTP, 1995].

Groups of male and female rats (CFE strain; 15/sex/group) were maintained on a diet containing 0 (control), 80, 400, or 4000-ppm *alpha*-amylcinnamaldehyde for 14 weeks. Additional groups of 5 male and 5 female rats were maintained on diets containing 400 and 4000 ppm *alpha*-amylcinnamaldehyde for 2 and 6 weeks. The respective mean dietary intakes over the 14-week period were reported to be 0, 6.1, 29.9 and 287.3 mg/kg bw/day for males and 0, 6.7, 34.9, and 320.3 mg/kg bw/day for females. Measurement of bodyweight, food and water consumption revealed no significant differences between treated and control groups. Hematological examinations (hemoglobin content, hematocrit, erythrocyte and leucocyte counts, and individual leucocyte counts) and blood chemistry determinations conducted at 2, 6, and 14 weeks revealed normal values. Reticulocyte counts performed only on control and the high dose groups showed no significant differences. Urinanalysis performed during the final week of treatment revealed no difference in cell content and renal concentration tests for test and control groups. Measurement of organ weights at autopsy revealed a statistically significant increase in relative liver weight in males ($p<0.01$) and females ($p<0.05$) at the 4000 ppm dietary level after 14 weeks, increased stomach weights in males at the 400 ppm level after 6 weeks, and increased relative kidney weight in males ($p<0.01$) at 4000 ppm after 14 weeks. The relative organ weight increases were not associated with any evidence of histopathology. Microscopic examination of prepared tissues from all major organs revealed no evidence of histopathological changes that could be associated with administration of the test material in the diet [Carpanini *et al.*, 1973].

Groups of male and female rats (15/sex) were maintained on a diet containing *alpha*-amylcinnamaldehyde at levels calculated to result in the approximate daily intake of 6.1 mg/kg bw for males and 6.6 mg/kg bw for females for a total of 90 days. Bodyweight measurements, food consumption, and observations of general condition were recorded regularly. Hematological and clinical chemistry examinations were conducted on 8 rats of each sex at week 6 and again on all animals at week 12 of experimentation. Neither measurements of growth, hematology, clinical chemistry, nor histopathology at necropsy revealed any evidence of toxic effects [Oser *et al.*, 1965].

Groups of male and female Sprague-Dawley rats (5/sex) received a 25 mg/kg dose of *alpha*-hexylcinnamaldehyde applied topically to the back daily for 9 days. Bodyweight measurements and observations of general condition were recorded regularly. At termination, hematological and clinical chemistry examinations, urinalysis, and liver and kidney weights were measured. Microscopic examination of liver, kidney, skin, and spinal cord were conducted. Neither measurements of growth, hematology, clinical chemistry, nor histopathology revealed any evidence of toxic effects [Moreno, 1981].

Dose levels of 0, 125, 250, 500, or 1000 mg/kg bw of *alpha*-hexylcinnamaldehyde were administered percutaneously to the backs of groups of albino rats (15/sex/group) daily for 90 days. Clinical observations and weekly body weight measurements showed a decreased survival in the 1000 mg/kg dose level and significantly decreased body weights in both sexes at 500 and 1000 mg/kg dosed groups. Hematological and clinical chemistry examinations conducted at week 6 and again on all animals at study termination revealed elevated white cell counts and segmented neutrophils in the two highest dose group of males and reduced lymphocyte counts only at the highest dose. In females, elevated white blood cell counts were reported in the three highest dosed groups, but only the 250 mg/kg group showed significantly reduced lymphocytes. Gross examination revealed irritation to the application site and gastrointestinal mucosa. Liver and kidney weights of females were significantly increased at 250, 500, and 1000 mg/kg dose levels. Histopathological examination revealed that the 1000 mg/kg dose level was associated with hepatic hydropic vacuolization and single cell degeneration, splenic lymphoid fibrosis, focal gastric ulceration, necrotizing dermatitis, and increased myeloid-erythroid upon bone marrow examination. A NOAEL of 125 mg/kg was reported [Lough *et al*., 1980].

In a study designed to evaluate the toxicity to the male and female reproductive systems, groups of SPF Fu albino male and female rats (14/sex/group) were given oral doses of 0, 2, 5, 25, or 50 mg/kg bw of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde daily by gavage in rape seed oil for 13 weeks. A satellite group at 50 mg/kg bw/day was maintained for an additional 4 weeks post treatment. Relative and absolute liver weights were increased in males marginally at 25 mg/kg bw/day and more significantly at 50 mg/kg bw/day. Females showed increased absolute and relative liver weight at 25 and 50 mg/kg bw/day

and increased absolute and relative adrenal weights at 50 mg/kg bw/day. However, these organ weight effects were reversible, in that after 4 weeks post treatment these was no difference between absolute and relative organ weights in treatment and control groups. Effects on spermatogenesis and spermiogenesis included, induction of spermatoceles in the cauda epididymidis, possible obstruction of the epididymal ducts, and significant number of Sertoli cell-only tubules in the 50 mg/kg bw/day group only. An NOAEL level for testicular effects was of 25 mg/kg bw/day [Givaudan-Roure, 1990c].

The study was repeated when 6 groups of albino Fu male (14/group) rats were given the same dose levels of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde daily by oral gavage for 13 weeks. An additional 50 mg/kg bw/day dose group was observed for 4 weeks post-treatment. Testes and epididymides of all male rats were subjected to microscopic examination. Treatment related histopathology revealed increased density of Leydig cells, spermatoceles and testicular atrophy in males, again only in the 50 mg/kg bw/day group [Givaudan-Roure, 1990d].

To determine if the testicular effects were species specific to the rat, groups of Beagle dogs (3/sex/group) were administered capsules containing 0, 4.4, 22.3, or 44.6 mg/kg bw *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde daily for 13 weeks. There was no evidence of toxicity in either sex based on daily observations, weekly measurement of body weights and food intake, hematological and clinical chemistry examination, urinanalysis, organ weight measurement, and complete histopathology evaluation [Givaudan-Roure, 1990b]. In a 9-week pilot study, 2 male beagle dogs were given oral doses of *p*-t-butyl-alpha-methyldihydrocinnamaldehyde at increasing dose level beginning at 50 ul/kg/day for the first week and reaching 400 ul/kg/day from weeks 4-8. At week 9, the dose was increased to 600 ul/kg/day. Histopathological examination revealed no significant changes to the any of the tissue, including the testes, evaluated [Givaudan-Roure, 1990e]. In a similar study, 3 female Beagle dogs were given capsules containing 200 mg/kg bw *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde daily for 13 weeks. Again no adverse effects were observed [Givaudan-Roure, 1990f].

Finally, 2 rhesus monkeys were given 100 mg/kg bw of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde administered in baby food daily for 5 days. Microscopic examination of the epididymides and testes failed to reveal any evidence of toxicity [Givaudan-Roure, 1990g]. The testicular and epididymal changes occurring in rats administered 50 mg/kg bw of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde by gavage 5 days per week for 90 days was not observed at 25 mg/kg bw and lower dose levels. Daily doses of 100 mg/kg bw for 5 days did not cause these effects in male mice, male guinea pigs, or male monkeys. Likewise no effects were observed after daily administration of 45 mg/kg bw to male (3) and female (3) dogs (beagles) 5 days per week for 90 days.

Plasma pharmacokinetic studies were performed after oral administration of 25 or 100 mg/kg bw of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde to rats. Peak plasma levels of 14.3 ug equivalents/ml at 3.5 hours and 52 ug equivalents/ml at 1.75 hours were achieved with the low and high dose, respectively, in male rats. The 0-48 hour Area Under the Curve (AUC) was 122 ug.hr/ml and 937 ug.hr/ml, respectively [Hawkins *et. al.*, 1995]. Peak plasma levels and AUC were also measured after dermal administration 16 mg of *p*-t-butyl-*alpha*-methylhydrocinnamaldehyde to humans. This dose was estimated to be approximately equivalent to a high-level exposure encountered in a cosmetic application. Peak plasma levels never exceeded the detection limit of 0.0.25 ug/ml and a theoretical "upper limit" AUC was estimated to be 0.3 ug.hr/ml [Hawkins *et. al.*, 1994]. Based on a comparison of peak plasma levels and AUC for humans and male rats, it was concluded that the adverse effect levels were at least 3 orders of magnitude greater than levels of exposure in humans under conditions of use. Also, no effect levels in rats occurred at dose levels at least 2 orders of magnitude greater than estimated human exposure.

3.4.4 Reproductive Toxicity

Reproductive studies on cinnamyl derivatives have concentrated on the parent alcohol, aldehyde, and acid. Rats were administered 5, 25, or 250 mg/kg bw/day cinnamaldehyde by gavage in olive oil on days 7 to 17 of gestation. A control group was included; however, it was not stated whether or not the controls received the olive oil vehicle. The number of dams treated per group was 15, 14, 16 and 15 for the control, low-, mid-, and high-dose groups, respectively. Fetal abnormalities observed included: poor cranial

ossification in all dose groups; increased incidences of dilated pelvis/reduced papilla in the kidney as well as dilated urethras in the low- and mid-dose groups; and an increase in the number of fetuses with two or more abnormal sternebrae in the mid-dose group. These effects are associated with apparent maternal toxicity as evidenced by a dose related decrease in weight gain at the two highest dose levels [Mantovani *et al.*, 1989].

Female rats were orally administered a 53.5 mg/kg bw dose of cinnamyl alcohol on either day four (implantation) or on days 10-12 (organogenesis) of gestation. On day 20 of gestation, all animals were terminated and fetuses removed for examination. Neither measurements of fetal bodyweight, length, nor survival number revealed any significant differences between test and control animals. Histopathological examinations revealed a slight reduction in skeletal ossification of the extremities. Examination of the sagittal sections revealed no anomalies in relation to palatal structure, eyes, brain, or other internal organs [Maganova and Zaitsev, 1973].

In a second study, female rats were orally administered a 53.5 mg/kg bw dose of cinnamyl alcohol once per day for the entire course of pregnancy. On day 20 of gestation, 50% of animals from both test and control groups were terminated and the fetuses removed for examination. Neither measurements of fetal bodyweight, liver nucleic acids, number of survivors, nor examination of bone development revealed any significant differences between test and control animals. The remaining females from both groups delivered normally. Neither measurements of offspring bodyweight, survival number, nor size and general development at birth or at one month revealed significant differences between test and controls [Zaitsev and Maganova, 1975].

In an additional study by the same authors, female rats were orally administered 0, 5, or 50 mg cinnamic acid/kg bw once daily for the entire course of pregnancy. On day 20 of gestation, 50% of the females from all groups were terminated and the fetuses removed for examination. Fetal body weight measurements, number of survivors, bone development, and hepatic nucleic acids were determined and no significant differences between test and control animals were noted. The remaining females from both treated and control groups delivered normally on days 22-23 of gestation. Neither measurements

of offspring bodyweight, size, survival number, nor general development at birth or one month following revealed any significant differences between test and control animals [Zaitsev and Maganova, 1975].

3.4.5 Developmental Toxicity

In an *in vivo* developmental toxicity assay, 50 time-mated CD-1 female mice received single oral doses of 1200 mg/kg of cinnamaldehyde in corn oil on days 6-13 of gestation. Female body weights were measured on days 6-15 of gestation and 3 days postpartum. Endpoints monitored included litter size, birth weight, neonatal growth, and survival to 3 days postpartum. Based on the measured parameters there was no significant difference between test and control groups [Hardin *et al*., 1987].

3.4.6 New Testing Required

Based on the consistent low acute oral and dermal toxicity in 29 studies, the "weight of evidence" that these substances exhibit no significant genotoxic potential in standardized *in vitro* and *in vivo* assays, the lack of any significant toxicity at dose levels many orders of magnitude greater than estimated levels of human exposure, and the lack of any reproductive or developmental effects in the absence of high-dose maternal toxicity, it is concluded that no additional testing is necessary for this chemical category.

3.5 Test Plan Table

Chemical	Physical-Chemical Properties				
	Melting Point	**Boiling Point**	**Vapor Pressure**	**Partition Coefficient**	**Water Solubility**
CAS No. 104-55-2 Cinnamaldehyde	NA	A	Calc	Calc	T,Calc
CAS No. 122-40-7 *alpha*-Amylcinnamaldehyde	NA	A	Calc	A	Calc
CAS No. 101-86-0 *alpha*-Hexylcinnamaldehyde	NA	A	A	A	Calc
CAS No. 80-54-6 *p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde	NA	A	Calc	A	T, A

Chemical	Environmental Fate and Pathways			
	Photodegradation	**Stability in Water**	**Biodegradation**	**Fugacity**
CAS No. 104-55-2 Cinnamaldehyde	Calc	Calc	R	Calc
CAS No. 122-40-7 *alpha*-Amylcinnamaldehyde	Calc	Calc	A	Calc
CAS No. 101-86-0 *alpha*-Hexylcinnamaldehyde	Calc	Calc	A	Calc
CAS No. 80-54-6 *p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde	Calc	A	A	Calc

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	**Acute Toxicity to Aquatic Invertebrates**	**Acute Toxicity to Aquatic Plants**
CAS No. 104-55-2 Cinnamaldehyde	Test, Calc	Test, Calc	Test, Calc
CAS No. 122-40-7 *alpha*-Amylcinnamaldehyde	Calc	Calc	Calc
CAS No. 101-86-0 *alpha*-Hexylcinnamaldehyde	Calc	Calc	Calc
CAS No. 80-54-6 *p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde	Test, Calc	Test, Calc	Test, Calc

Chemical	Human Health Data					
	Acute Toxicity	**Genetic Toxicity *In Vitro***	**Genetic Toxicity *In Vivo***	**Repeat Dose Toxicity**	**Repro-ductive Toxicity**	**Develop-mental Toxicity**
CAS No. 104-55-2 Cinnamaldehyde	A	A	A	A	A	A
CAS No. 122-40-7 *alpha*-Amylcinnamaldehyde	A	A	A	A	R	R
CAS No. 101-86-0 *alpha*-Hexylcinnamaldehyde	A	A	A	A	R	R
CAS No. 80-54-6 *p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde	A	A	A	A	R	R

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

4 References for Test Plan and Robust Summaries

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AR 201-12912B

The Flavor and Fragrance High Production Volume Consortia

Robust Summaries for Cinnamyl Derivatives

FFHPVC Aromatic Consortium Registration Number

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al.*, 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 Chemical and Physical Properties

1.1 Melting Point

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Method/guideline	Mean or weighted
Melting Point	**0.04** °C
Remarks for Data	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Mean or weighted
Melting Point	**33.9** °C
Remarks for Data	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinnamaldehyde

CAS No.	101-86-O
Method/guideline	Mean or weighted
Melting Point	44.4 °C
Remarks for Data	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Mean or weighted
Melting Point	46.3 °C
Remarks for Data	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinrmnaldehyde
CAS No.	**10** l-86-0
Melting Point	4 °C
References	Fenaroli's Handbook of Flavor Ingredients Volume II 3rd Edition. Edited by G. Burdock. CRC Press, 1994, Reston VA,

1.2 Boiling Point

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Boiling Point	250 °C
Remarks for Test Conditions	No test conditions provided
References	Fragrance Materials Association (FMA)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7

Boiling Point	**284 °C**
Remarks for Test Conditions	No test conditions provided
References	Fragrance Materials Association (FMA)

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Boiling Point	226.7 °C
Method/guideline	Stein and Brown Method
Remarks for Test Conditions	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Boiling Point	304.8 °C
Method/guideline	Stein and Brown Method
Remarks for Test Conditions	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Boiling Point	305 °C
Remarks for Test Conditions	No test conditions provided
References	Fragrance Materials Association (FMA)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Boiling Point	318.7 °C
Method/guideline	Stein and Brown Method
Remarks for Test Conditions	Calculated

References	Syracuse Research Corporation (SRC)

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Boiling Point	**280 °C**
Method/guideline	Stein and Brown Method
Remarks for Test Conditions	Calculated
References	Syracuse Research Corporation (SRC)

Substance Name	p-t-Butyl-alpha-methylhydrocinnamaldehyde
CAS No.	80-54-6
Boiling Point	258°C
References	Arctander's Perfume and Flavor Chemicals Vol. I Publisher: S. Arctander (1969) Montclair, NJ

1.3 Vapor Pressure

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Calculated
GLP	NA
Vapor Pressure	0.02mm Hg (0.00267 kPa)
Temperature	20 °C
References	Fragrance Materials Association (FMA)

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Modified Antoine and Grain Method
GLP	NA
Vapor Pressure	0.09 mm Hg (0.012 kPa)

Temperature	**20** °C
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	**122-40-7**
Method/guideline	Calculated
GLP	NA
Vapor Pressure	<0.001 mm Hg (~0.00013 kPa)
Temperature	**20** °C
References	Fragrance Materials Association (FMA)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Modified Grain Method
GLP	**N A**
Vapor Pressure	0.0012 mm Hg ((0.00016 kPa)
Temperature	**20** °C
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
GLP	NA
Year	**1995**
Vapor Pressure	**0.0002** mg Hg (0.000027 kPa)
Temperature	**20** °C
References	Vuilleumier C., Flament, I., Sauvegrain, P. (1995) Headspace measurement of evaporation rates of perfumes applied onto the skin: Application to rose essential oils and their principal components. Perfumer and Flavorish 20(2), I-Q.

Substance Name	alpha-Hexylcinnamaldehyde

CAS No.	101-86-O
Method/guideline	Calculated
GLP	NA
Vapor Pressure	<0.001 mm Hg (~0.00013 kPa)
Temperature	**20** °C
References	Fragrance Materials Association (FMA)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Modified Grain Method
GLP	NA
Vapor Pressure	0.00048 mm Hg (0.000064 kPa)
Temperature	**20** °C
References	Syracuse Research Corporation (SRC)

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Modified Grain Method
GLP	NA
Vapor Pressure	0.00358 mm Hg (0.00048 kPa)
Temperature	**20** °C
References	Syracuse Research Corporation (SRC)

1.4 Octanol/Water Partition Coefficient

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	OECD Guideline No. 117
GLP	**Yes**

Year	1994
Log Pow	5.3
Temperature	24 °C
Remarks for Data Reliability	Guideline study. The log Kow compares well with the calculated value. Data are considered reliable.
Data Quality Reliabilities	Reliability 1. Reliable without restriction.
References	Givaudan-Roure (1994d) Partition coefficient n-octanol/water of alpha-hexylcinnamaldehyde. Unpublished report to RIFM.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
GLP	NG
Year	NG
Method/guideline	Calculated
Partition coefficient	1.82
Remarks for Data Reliability	Comparable to guidelines/standards.
Data Quality Reliabilities	Reliability code 2. Reliable with restrictions
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
GLP	Yes
Year	1994
Method/guideline	OECD Guideline No. 117
Log Pow	4.7
Temperature	24 °C
Remarks for Data Reliability	Guideline study. The log Kow compares well with the calculated value. Data are considered reliable.
Data Quality Reliabilities	Reliability code 1. Reliable without restriction.
References	Givaudan-Roure (1994a) Partition coefficient n-octanol/water of alpha-amylcinnamaldehyde. Unpublished report to RIFM.

Substance Name	alpha-Amylcinnamaldehyde

CAS No.	122-40-7
GLP	**NG**
Year	**NG**
Method/guideline	Calculated
Log Pow	4.33
Remarks for Data Reliability	Comparable to guidelines/standards,
Data Quality Reliabilities	Reliability code 2. Reliable with restrictions.
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
GLP	**NG**
Year	**NG**
Method/guideline	Calculated
Log Pow	4.82
Remarks for Data Reliability	Comparable to guidelines/standards.
Data Quality Reliabilities	Reliability code 2. Reliable with restrictions.
References	Syracuse Research Corporation (SRC)

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
GLP	**NG**
Year	**1996**
Method/guideline	Measured
Log Pow	**4.9**
Remarks for Data Reliability	Comparable to guidelines/standards.
Data Quality Reliabilities	Reliability code 2. Reliable with restrictions.
References	Quest (1994) Private communication to FMA.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
GLP	**NG**
Year	**NG**
Method/guideline	Calculated
Log Pow	**4.36**
Remarks for Data Reliability	Comparable to guidelines/standards.
Data Quality Reliabilities	Reliability code 2. Reliable with restrictions.
References	Syracuse Research Corporation (SRC)

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
GLP	Yes
Year	1994
Method/guideline	OECD Guideline No. 117
Log Pow	4.2
Temperature	24 °C
Remarks for Data Reliability	Guideline study. The log Kow compares well with the calculated value. Data are considered reliable.
Data Quality Reliabilities	Reliability 1. Reliable without restriction.
References	Givaudan-Roure (1994b) Partition coefficient n-octanol/water of p-t-butyl-alpha-methyldihydrocinnamic aldehyde. Unpublished Report to RIFM.

1.5 Water Solubility

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Method/guideline	Calculated at log Kow=1.90 (ESPKOW)
Value (mg/L) at temperature	2150 mg/L
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.

References	ESPOW

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Calculated at log Kow=4.33 (ESPKOW)
Value (mg/L) at temperature	8.5 mg/L
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.
References	ESPKOW

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Calculated at log Kow=4.82 (ESPKOW)
Value (mg/L) at temperature	2.75 mg/L
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.
References	ESPKOW

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaidehyde
CAS No.	80-54-6
Year	**1995**
Method/guideline	OECD 105
Value (mg/L) at temperature	33 mg/L at 20 °C
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 1. Reliable without restrictions.
References	Givaudan-Roure (1995) Water solubility of *p*-t-butyl-alpha-methylhydrocinnamic aldehyde. Unpublished Report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Year	**1994**
Method/guideline	**NG**
Value (mg/L) at temperature	<100 mg/L at 20 °C

Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.
References	Givaudan-Roure (1995) Water solubility of *p*-t-butyl-alpha-methylhydrocinnamic aldehyde. Unpublished Report to RIFM

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Year	**1990**
Method/guideline	**NG**
Value (mg/L) at temperature	0.02% w/v (200 mg/L)
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.
References	Bush Boake Allen (BBA) (1990). Biodegradability of p-t-butyl-alpha-methylhydrocinnamic aldehyde and methyl-alpha-ionone. Unpublished report to RIFM.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Calculated at log Kow= 4.36 (ESKOW)
Value (mg/L) at temperature	7.8 mg/L
Remarks for Data Reliability	Comparable to guidelines/standards. Reliability code 2. Reliable with restrictions.
References	ESPKOW

2 Environmental Fate and Pathways

2.1 Photodegradation

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Calculation
Test Type	AOPWIN
Halflife t1/2	3.17
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.

References	AOPWIN

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Calculation
Test Type	AOPWIN
Halflife t1/2	2.40 hrs
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	AOPWIN

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Calculation
Test Type	AOPWIN
Halflife t1/2	2.33 hrs
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	AOPWIN

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Calculation
Test Type	AOPWIN
Halflife t1/2	3.88 hrs
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	AOPWIN

2.2 Biodegradation

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamic aldehyde, 91-98% pure, clear, almost colorless liquid, fresh, light, green floral, reminiscent of lily; strongly diffusive
CAS No.	80-54-6
Method/guideline	Method F
Test Type	DOC - Method F from Blue book series, 1981
GLP	N G
Year	1990
Contact Time (units)	28 days
Innoculum	Activated sludge from local STP
Remarks for Test Conditions	50.04 mg DOC/L at 20 C for 28 days
Degradation % after time	96% at 31 days
Results	92 % biodegradation after 28 days. 96% after day 31.
Time required for 10% degradation	<1 day
10 day window criteria	Yes
Total degradation	Yes
Conclusion Remarks	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with **OECD** 301 F guidelines.
References	Bush Boake Allen (BBA) (1990). Biodegradability of *p*-t-butyl-alpha-methylhydrocinnamic aldehyde and methyl-alpha-ionone. Unpublished report to RIFM.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Methodlguideline	Biodegradability was determined by sealed vessel test based on OECD Guideline 301 B.
Test Type	OECD 301 B CO2 evolution
GLP	**Yes**
Year	**1996**
Contact Time (units)	28 days

Innoculum	Secondary effluent from an unacclimatized activate
Degradation % after time	65% at 28 days
Time required for 10% degradation	9 days
10 day window criteria	Yes
Total degradation	No
Conclusion Remarks	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with OECD 301 B guidelines.
References	Givaudan-Roure (1989) Ready Biodegradability of Amyl Cinnamic Aldehyde according to OECD Guideline No. 301 B Private Communication to FMA.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Ready biodegradability of amyl acinnamic aldehyde was determined according to OECD Guideline No. 301 F.
Test Type	OECD No. 301 F Respirometric method/ SAPROMAT
GLP	Yes
Year	1992
Contact Time (units)	28 days
Innoculum	Activated sludge
Remarks for Test Conditions	Bottle 1 & 2: Basal culture medium + activated sludge 30 mg/l + test chemical (100 mg/l); Bottle 3: Basal culture medium + activated sludge 30mg/l+aniline (100mg/l); Bottle 4: Basal culture medium + activated sludge 30 mg/l.
Degradation % after time	90% in 28days
Results	90% of the test chemical was biodegraded in 28 day as compared to only 61% of reference material (aniline) was biodegraded in 28 days.
Total degradation	Yes
Conclusion Remarks	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with OECD 301 F guidelines.
References	Givaudan Roure (1992a). Ready Biodegradability of Amyl Cinnamic Aldehyde according to OECD Guideline No. 301 F. Unpublished report to RIFM.

Substance Name	alpha-Hexylcinnamalclehyde: Pale yellow oily liquid with sweet slightly floral odor.
CAS No.	101-86-o
Method/guideline	Sealed vessel test: based on OECD Guideline 3018
Test Type	OECD 301B CO2 evolution
GLP	Yes
Year	1994
Contact Time (units)	28 days
Innoculum	Secondary effluent from unacclimatized activated sludge plant
Remarks for Test Conditions	Test concentration: 11.9 mg/l organic carbon. Test temp: 20-24 °C
Degradation % after time	76.5% at 28 days
Results	76.5% biodegradable (95% Cl-67.0-85.9) in 28 days,
Time required for 10% degradation	<11 days
10 day window criteria	No
Total degradation	No
Conclusion Remarks	The test substance achieved the 60% pass level by day 28 but failed the 10 day window criterium and therefore can be classified as ultimately biodegradable according to this test protocol.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with OECD 301 B guidelines.
References	Quest (1994) Report on Hexyl Cinnamic Aldehyde Biodegradation.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Ready Biodegradability of the test material was determined according to OECD Guideline No. 301 F
Test Type	OECD No. 301 F, Respirometric method
GLP	**Yes**
Year	**1992**
Contact Time (units)	28 days
Innoculum	Activated sludge

Remarks for Test Conditions	Bottle 1 & 2: Basal culture medium + activated sludge 30 mg/l + test chemical (-100 mg/l). Bottle 3: Basal culture medium + activated sludge 30 mg/l + aniline (-100 mg/l); Bottle 4: Basal culture medium + activated sludge 30 mg/l.
Degradation % after time	97% in 28 days
Results	97% of the test material was biodegraded in 28 days as compare to 61% of aniline in the same period.
Total degradation	Yes
Conclusion Remarks	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with OECD 301F guidelines.
References	Givaudan Roure. (1992b). Ready Biodegradability of Hexyl Cinnamic Aldehyde according to OECD Guideline No. 301F. Unpublished report to RIFM.

Substance Name	alpha-Hexylcinnamaldehyde 94% pure ▪ 44% cis and 50% trans
CAS No.	5392-40-5
Test Type	OECD 301 B CO2 evolution
GLP	No
Year	1994
Contact Time (units)	28 days
Innoculum	Secondary effluent from sludge from local STP
Remarks for Test Conditions	IO mg/l organic carbon at 20 °C for 28 days
Degradation % after time	92.1% at 28 days
Results	92.1% biodegradation in 28 days
Time required for 10% degradation	<4 days
10 day window criteria	Yes
Total degradation	No
Conclusion Remarks	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	The study was conducted in accordance with OECD 301 B guidelines.
References	Quest (1994) Private communication to FMA.

2.3 Fugacity

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Air-Water Partition Coefficient
Absorption Coefficient	0.0099
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Soil-Water Partition Coefficient
Absorption Coefficient	986
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.1 I. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach.

Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Sediment-Water Partition Coefficient
Absorption Coefficient	1970
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Suspended Sediment-Water Partition Coefficient
Absorption Coefficient	6160
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach, Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Fish-Water Partition Coefficient
Absorption Coefficient	2510
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Aerosol-Air Partition Coefficient
Absorption Coefficient	9570000
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach, Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	*alpha*-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Air
Estimated Distribution and Media Concentration	9.7%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Water
Estimated Distribution and Media Concentration	1.94%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
GAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Soil
Estimated Distribution and Media Concentration	86.4%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Sediment
Estimated Distribution and Media Concentration	1.92%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.06%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Fish
Estimated Distribution and Media Concentration	0.0049%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, VP, estimated MP
Media	Aerosol
Estimated Distribution and Media Concentration	0.0018%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air-Water Partition Coefficient
Absorption Coefficient	0.022
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
GAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil-Water Partition Coefficient
Absorption Coefficient	3230
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	*alpha*-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment-Water Partition Coefficient
Absorption Coefficient	7850
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment-Water Partition Coefficient
Absorption Coefficient	24500
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish-Water Partition Coefficient
Absorption Coefficient	9980
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol-Air Partition Coefficient
Absorption Coefficient	14100000
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air
Estimated Distribution and Media Concentration	5.7%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Water
Estimated Distribution and Media Concentration	0.52%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil
Estimated Distribution and Media Concentration	91.7%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment
Estimated Distribution and Media Concentration	2.0%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test **Type**	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.064%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish
Estimated Distribution and Media Concentration	0.0052%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.0016%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach, Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Model Conditions	**25 °C,** 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air-Water Partition Coefficient
Absorption Coefficient	**0.0031**
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Model Conditions	**25 °C,** 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil-Water Partition Coefficient
Absorption Coefficient	1.30
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment-Water Partition Coefficient
Absorption Coefficient	2.60
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment-Water Partition Coefficient
Absorption Coefficient	8.12
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Model Conditions	**25** °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish-Water Partition Coefficient
Absorption Coefficient	**3.30**
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Model Conditions	**25** °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol-Air Partition Coefficient
Absorption Coefficient	**483000**
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air
Estimated Distribution and Media Concentration	12.7%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test **Type**	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Water
Estimated Distribution and Media Concentration	82.4%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil
Estimated Distribution and Media Concentration	4.82%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment
Estimated Distribution and Media Concentration	0.11%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.0034%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish
Estimated Distribution and Media Concentration	0.00027%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.00012%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by **a** recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air-Water Partition Coefficient
Absorption Coefficient	0.001
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil-Water Partition Coefficient
Absorption Coefficient	312
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test **Type**	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment-Water Partition Coefficient
Absorption Coefficient	624
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment-Water Partition Coefficient
Absorption Coefficient	1950
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish-Water Partition Coefficient
Absorption Coefficient	792
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

Multimedia environmental models: The fugacity approach, Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol-Air Partition Coefficient
Absorption Coefficient	15000000
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test **Type**	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Air
Estimated Distribution and Media Concentration	**3.2%**
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Water
Estimated Distribution and Media Concentration	6.3%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacit-y-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 "C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Soil
Estimated Distribution and Media Concentration	88.5%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Sediment
Estimated Distribution and Media Concentration	2.0%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Model Conditions	25 °C, 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.061%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

	Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Model Conditions	**25 °C,** 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Fish
Estimated Distribution and Media Concentration	0.0050%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

Substance Name	p-t-butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Model Conditions	**25 °C,** 100,000 lbs
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level 1
Input Parameters	MW, log Kow, water solubility, MP, estimated VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.0010%
Data Qualities Reliabilities	Reliable with restriction
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991)

Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL

3 Ecotoxicity

3.1 Acute Toxicity to Fish

Substance Name	Cinnamic aldehyde
CAS No.	104-55-2
Method/guideline	ECOSAR
Test Type	Calculated based on log Kow
Species/Strain/Supplier	Fish
Exposure period	96 hr
Conclusion Remarks	LC50 = 11.9 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	ECOSAR
Test Type	Calculated based on measured Kow
Species/Strain/Supplier	Fish
Exposure period	96 hr
Conclusion Remarks	LC50 = 3.14 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method but are not consistent with chemical structure. Data are considered overly conservative.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-0
Method/guideline	ECOSAR
Test **Type**	Calculated based on measured Kow

Species/Strain/Supplier	Fish
Exposure period	**96 hr**
Conclusion Remarks	LC50 = 2.36 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method but are not consistent with chemical structure. Data are considered overly conservative.

Substance Name	*p*-tert-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	ECOSAR
Test Type	Calculated based on measured Kow
Species/Strain/Supplier	Fish
Exposure period	96 hr
Conclusion Remarks	LC50 = 3.19 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method but are not consistent with chemical structure. Data are considered overly conservative.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	ECOSAR
Test Type	Calculated based on log Kow
Species/Strain	Daphnia magna
Test Details	48 hrs
Remarks for Results	LC50 = 8.1 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

Substance Name	alpha-Amylcinnamaldehyde

CAS No.	122-40-7
Method/guideline	**ECOSAR**
Test Type	Calculated based on measured Kow
Species/Strain	Daphnia magna
Test Details	**48** hrs
Remarks for Results	LC50 = 0.42 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	ECOSAR
Test Type	Calculated based on measured Kow
Species/Strain	Daphnia magna
Test Details	**48** hrs
Remarks for Results	LC50 = 0.22 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

Substance Name	*p*-tert-Butyl-*alpha*-methyldihydrocinnamic aldehyde
CAS No.	80-54-6
Method/guideline	ECOSAR
Test **Type**	Calculated based on measured Kow
Species/Strain	Daphnia magna
Test Details	**48** hrs
Remarks for Results	LC50 = 0.40 mg/l
Remarks for Data Reliability	The data are obtained by **a** recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

3.3 Acute Toxicity to Aquatic Plants

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Test compounds were dissolved under sterile conditions in modified KNOP solution. Subsequently, these solutions were measured into a flask to which a growing cell suspension was added. Cultures were shaken for 48 hr, where after the cells were centrifuges.
Species/Strain/Supplier	Chlorella vulgaris
Exposure period	96 hrs
Remarks for Test Conditions	After acidification to 4.0 aqueous solution was extracted w/ ether. Ether fractions were treated w/anhydrous sodium sulfate, filtered & concentrated. Ethanol was added to obtain a final extract of 1 ml. From this extract, a sample was subjected to TLC.
Biological Observations	Cinnamic aldehyde was found to inhibit the algae growth in a concentration as low as 5X10(-5) M. At the same concentration a stimulation of the respiration of the algae was observed at pH 5.6 & pH 7.2
Conclusion Remarks	Cinnamic aldehyde inhibited the algal growth and stimulated the respiration.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Dedoner, A. and VanSumere, CF. (1971). The effect pf phenolics and related compounds on the growth and the respiration of Chlorella vulgaris. Z. PflPhysiol 65(1): 70-80.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Calculated
Test Type	ECOSAR
Species/Strain/Supplier	Green algae
Exposure period	96 hrs
Conclusion Remarks	EC50 = 0.87 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Calculated
Test Type	ECOSAR
Species/Strain/Supplier	Green algae
Exposure period	96 hrs
Conclusion Remarks	EC50 = 0.34 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

Substance Name	p-tert-Butyl-alpha-methyldihydrocinnamic aldehyde
CAS No.	80-54-6
Method/guideline	Calculated
Test Type	ECOSAR
Species/Strain/Supplier	Green algae
Exposure period	96 hrs
Conclusion Remarks	EC50 = 0.827 mg/l
Remarks for Data Reliability	The data are obtained by a recognized SAR calculation method and are consistent with chemical structure. Data are considered reliable.
References	ECOSAR

4 Human Health Data

4.1 Acute Toxicity

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	LD50 was computed by method of Litchfield & Wilcoxon (1949).

Test Type	Acute Oral LD50
GLP	Not reported
Year	1964
Species/Strain	Guinea pig
Sex	Male and Female
# of animals per sex per dose	N G
Route of administration	Oral
Value LD50 or LC50 with confidence limits	LD50 = 1160 (95% CI 950-1420) mg/kg.
Remarks for Results	The LD50 was reported to be 1160 mglkg. Coma was reported with higher doses.
Conclusion Remarks	The LD50 was reported to be 1160 (95%CI 950-1420) mglkg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal Food Cosmetic Toxicology,
References	Jenner, P. M., Hagan, E.C., Taylor, J.M, Cook, E.L. and Fitzhugh, O.G. (1964). Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity. Food and Cosmetics Toxicology 2(3): 327-343.

Substance Name	Cinnamaldehyde
GAS No.	104-55-2
Method/guideline	A group of animals, 6 animals per group per sex were given the test substance by oral gavage.
Test Type	Acute Oral LD50 test
GLP	N G
Year	1974
Species/Strain	Rat/White
Sex	Male and Female
# of animals per sex per dose	6
Vehicle	Sunflower oil
Route of administration	Oral (gavage)
Remarks for Test Conditions	No other details were given
Value LD50 or LC50 with confidence limits	LD50 = 3400 mglkg or 25.8 mM.
Remarks for Results	No other details were given

Conclusion Remarks	The oral LD50 value for cinnamaldehyde was calculated to be 3400 mg/kg
Data Qualities Reliabilities	Reliability code 3. Data not reliable. The data must be viewed with caution.
Remarks for Data Reliability	Original article is in Russian. English translation doesn't report details or these details are missing in the original article.
General Remarks	Authors claim that the acute oral LD50 values for Cinnamaldehyde for rats, mice and guinea pigs was the same value of 3400 mg/kg.
References	Zaitsev, A, N. and Rakhmanina (1974). Some Data on the Toxic Properties of Phenylethyl and Cinnamyl Alcohol Derivatives. Vopr. Pitaniya 6: 48-53.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	A group of animals, 6 animals per group per sex were given the test substance by oral gavage.
Test Type	Acute Oral LD50 test
GLP	N G
Year	1974
Species/Strain	Mice/White
Sex	Male and Female
# of animals per sex per dose	6
Vehicle	Sunflower oil
Route of administration	Oral (gavage)
Remarks for Test Conditions	No additional details given.
Value LD50 or LC50 with confidence limits	LD50 = 3400 mg/kg or 25.8 mM.
Remarks for Results	No other details were given
Conclusion Remarks	The oral LD50 value for cinnamaldehyde was calculated to be 3400 mg/kg
Data Qualities Reliabilities	Reliability code 3. Data not reliable.
Remarks for Data Reliability	Original article was in Russian. English translation either doesn't report details or these details are missing in the original article.
General Remarks	Authors claim that the acute oral LD50 values for Cinnamaldehyde for rats, mice and guinea pigs was same value of 3400 mg/kg.
References	Zaitsev, A, N. and Rakhmanina (1974). Some Data on the Toxic Properties of Phenylethyl and Cinnamyl Alcohol Derivatives. Vopr. Pitaniya 6: 48-53.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	A group of animals, 6 animals per group per sex were given the test substance by oral gavage.
Test Type	Acute Oral LD50 test
GLP	N G
Year	1974
Species/Strain	Guinea pig
Sex	Male and Female
# of animals per sex per dose	6
Vehicle	Sunflower oil
Route of administration	Oral (gavage)
Remarks for Test Conditions	No additional details given.
Value LD50 or LC50 with confidence limits	LD50 = 3400 mg/kg or 25.8 mM.
Remarks for Results	No other details given
Conclusion Remarks	The oral LD50 value for cinnamaldehyde was calculated to be 3400 mg/kg
Data Qualities Reliabilities	Reliability code 3. Data not reliable. The data must be viewed with caution.
Remarks for Data Reliability	Original article was in Russian. English translation either doesn't report details or these details are missing in the original article
General Remarks	Authors claim that the acute oral LD50 values for Cinnamaldehyde for rats, mice and guinea pigs was same value of 3400 mg/kg.
References	Zaitsev, A, N. and Rakhmanina (1974). Some Data on the Toxic Properties of Phenylethyl and Cinnamyl Alcohol Derivatives. Vopr. Pitaniya 6: 48-53.

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Method/guideline	The study was performed on albino rabbits according to the method described under section 191.10 of the final order enforcement Regulation, Federal Register Vol. 26, No. 155, p7336, Aug 12, 1961.
Test Type	Acute Dermal LD50
GLP	Not reported
Year	**1973**

Species/Strain	Rabbit/Albino
Sex	Not reported
# of animals per sex per dose	20
Vehicle	None reported
Route of administration	Dermal
Remarks for Test Conditions	The test substance was applied to the intact or abraded skin of the rabbit. The mortality data was evaluated according to the Thompson moving method as described by Carrol S. Weil. Biometrics 8(3): 249-263, 1952. Doses tested 0.25, 0.50, 1.0, 2.0 & 4.0 ml/kg.
Value LD50 or LC50 with confidence limits	Acute Dermal LD50 & 19120 Confidence Limit = 0.59 (0.42-0.84) ml/kg. LD50=620 mg/kg bw.
Number of deaths at each dose level	0.25 ml/kg 0/2 death (Intact or abraded); 0.50 ml/kg- 1/2 deaths in abraded group; 1 .O ml/kg- 2/2 deaths in both intact & abraded group; 2.0 ml/kg- 2/2 deaths in both intact and abraded group; 4.0 ml/kg- 212 deaths in both intact & abraded group.
Conclusion Remarks	Cinnamic aldehyde has an acute dermal LD50 and 19/20 Confidence limits of 0.59 0.42-0.884) ml/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Shelanski, M. and Moldovan, M. (1973). Report to RIFM by Food and Drug Research Laboratories. Feb 16, 1973.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Rabbits were dosed dermally with cinnamic aldehyde at 0.59, 0.83, 1.00, 1.23 & 1.50 ml/kg. The test substance was kept in contact with the skin for 24 hours. The animals were observed daily for signs of mortality, toxicity and pharmacological effects.
Test Type	Acute Dermal Toxicity
GLP	Yes
Year	1986
Species/Strain	New Zealand Albino rabbits
Sex	Male and Female
# of animals per sex per dose	4
Route of administration	Dermal
Remarks for Test Conditions	Skin reactions were scored on days 1, 7 and 14. Body weights were recorded pretest and at termination. All animals were examined for gross pathology. The LD50 was calculated by the method of Litchfield and Wilcoxon.
Value LD50 or LC50 with confidence limits	The LD50 and 95% confidence limits are: 1.2 (0.9 - 1.6) ml/kg of the body weight.

Number of deaths at each dose level	0.59 ml/kg= 0 dead/2 treated; 0.83 ml/kg = 2 dead/4 treated; 1 .00 ml/kg = 1 dead/4 treated; 1.23 ml/kg = 1 dead/4 treated; 1.50 ml/kg = 4 dead/4 treated.
Remarks for Results	Deaths occurred by day 3, and were preceded with predeath physical signs of few feces, lethargy, ataxia and rales. Necropsy of the deaths revealed abnormalities of the lungs, liver, kidneys, treated skin and GI tract, **as** well as brown staining of the anogenital area and yellow staining of the nose/mouth area. Survivors: signs of diarrhea, few feces, emaciation, ataxia and limited mobility due to severe skin reaction, abnormalities of skin and intestines. Larger than normal uterus.
Conclusion Remarks	The LD50 and 95% confidence limits are: 1.2 (0.9 - 1.6) ml/kg of the body weight. LD50=1260 mg/kg bw
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP
References	Fritzsche Dodge and Olcott, Inc. (1986). Acute Dermal Toxicity of Cinnamaldehyde in Rabbits. Unpublished. Report to RIFM.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Acute oral toxicity was determined in rats.
Test Type	Acute Oral Toxicity
GLP	N G
Year	1977
Species/Strain	Rats
Sex	Not reported
# of animals per sex per dose	1 0
Route of administration	Oral
Remarks for Test Conditions	Doses used: 1.22, 2.47, 5.0 and 10.14 g/kg
Value LD50 or LC50 with confidence limits	The oral LD50 and 95% confidence interval are 3.7 (2.654) g/kg
Number of deaths at each dose level	1.22 g/kg=0/10; 2.47 g/kg= 1110; 5.0 g/kg= 7/10; 10.14 g/kg = 10/10
Remarks for Results	Toxic signs = 1.22 g/kg: diarrhea; 2.47 g/kg: piloerection, lethargy, flaccid; 5.0 g/kg: lethargy, piloerection, diarrhea, coma; 10.14 g/kg: ataxia, lethargy, piloerection and diarrhea.
Conclusion Remarks	The oral LD50 and 95% confidence interval are 3.7 (2.654) g/kg. LD50=3700 mglkg bw.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Moreno 0. M. (1977b). Acute Oral toxicity in Rats. Dermal Toxicity in Rabbits. Unpublished. Report to RIFM.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	40 Male Wistar rat strain were used. Rats were observed for signs of toxicity and pharmacologic effect at 1, 6 & 24 hours and daily thereafter for a period of 14 days.
Test Type	Oral LD50
GLP	NG
Year	1971
Species/Strain	Male Wistar rats
Sex	Male
# of animals per sex per dose	10
Route of administration	Oral
Remarks for Test Conditions	Doses tested: 1.78, 2.67, 4.0 and 6.0 gm/kg.
Value LD50 or LC50 with confidence limits	LD50 (95% Confidence Limit) = 3.1 (3.75-2.45) g/kg
Number of deaths at each dose level	1.78 g/kg = 1/10; 2.67 glkg = 4/10; 4.0 g/kg = 7/10; 6.0 g/kg = IO/IO.
Remarks for Results	Symptomology: Depression, Lethargy, Anorexia, Weight loss
Conclusion Remarks	The oral LD50 was reported to be 3.1 g/kg. LD50=3100 mg/kg bw.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Moreno O.M. (1971) Acute toxicity studies in rats, mice, rabbits and guinea pigs. Unpublished report to RIFM.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Acute Dermal toxicity
Test Type	Acute Dermal LD50
GLP	Not reported
Year	**1972**
Species/Strain	Rabbits
Sex	Not reported
# of animals per sex per dose	6

Vehicle	Not reported
Route of administration	Dermal
Remarks for Test Conditions	Dose tested = 5.0 g/kg
Value LD50 or LC50 with confidence limits	Dermal LD50 <5.0 g/kg.
Number of deaths at each dose level	All animals died overnight after dosing.
Conclusion Remarks	The dermal LD50 value for cinnamic aldehyde in rat is less than 5 g/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Shelanski M. and Moldovan, M. (1973). Report to RIFM by Food and Drug Research Laboratories. Feb 16, 1973.Shelanski, M. and Moldovan, M. (1973). Report to RIFM by Food and Drug Research Laboratories. Feb 2, 1973.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Rabbits were dosed dermally with 1000 mg/kg of the test material and kept in contact with the skin for 24 hours. Dermal responses were recorded 24 hours, day 7 and 14 postdose.
Test Type	Dermal LD50
GLP	Yes
Year	1996
Species/Strain	New Zealand White rabbits
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	NG
Route of administration	Dermal
Remarks for Test Conditions	Body weights were recorded pretest and at death, or termination in the survivors. All animals were examined for gross pathology. The test sites were scored using the numerical Draize scoring code. An estimate of the LD50 was made based on the survival during the study.
Value LD50 or LC50 with confidence limits	The LD50 is greater than 1000 mg/kg of body weight.
Number of deaths at each dose level	All animals survived the 1000 mg/kg dermal application.
Remarks for Results	Necropsy revealed treated skin abnormalities in all animals. Liver abnormalities were noted in one animal, and kidney abnormalities in three animals, one of which had wetness of the anogenital area.
Conclusion Remarks	The dermal LD50 was reported to be greater than 1000 mglkg.

Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	MB Research Labs (1996) Unpublished Report to RIFM.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Oral LD50
Test Type	Acute Oral LD50
GLP	Not reported
Year	1965
Species/Strain	Rats
Sex	Not reported
# of animals per sex per dose	NG
Vehicle	NG
Route of administration	Oral
Remarks for Test Conditions	Article in Romanian. Details not given in the English abstract.
Value LD50 or LC50 with confidence limits	LD50 = 3350 mglkg.
Number of deaths at each dose level	Article in Romanian. Details not given in the English abstract.
Remarks for Results	Article in Romanian. Details not given in the English abstract.
Conclusion Remarks	LD50 = 3.350 mglkg
Data Qualities Reliabilities	Reliability code 3. Data not reliable.
Remarks for Data Reliability	Article in Romanian. Details not given in the English abstract,
References	Sporn A. (1965). Investigation of the Toxicity of Cynamic Aldehyde. Igiena 14(6): 339-346.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	LD50
Test Type	Intraperitoneal LD50
GLP	Not reported

Year	**1965**
Species/Strain	Mice
Sex	Not reported
# of animals per sex per dose	N G
Vehicle	N G
Route of administration	Intraperitoneal
Remarks for Test Conditions	Article in Romanian. Details not given in the English abstract.
Value LD50 or LC50 with confidence limits	LD50 = 2318 mg/kg.
Remarks for Results	Article in Romanian. Details not given in the English abstract.
Conclusion Remarks	Intraperitoneal LD50 for Cinnamaldehyde in mice was shown to be 2318 mg/kg.
Data Qualities Reliabilities	Reliability code 3. Data not reliable.
Remarks for Data Reliability	Article in Romanian. Details not given in the English abstract.
References	Sporn A. (1965). Investigation of the Toxicity of Cynamic Aldehyde. Igiena 14(6): 339-346.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	LD50 was computed by method of Litchfield & Wilcoxon (1949).
Test Type	Acute Oral LD50
GLP	Not reported
Year	1964
Species/Strain	Osborne-Mendel rats
Sex	Male and Female
# of animals per sex per dose	1 0
Vehicle	None
Route of administration	Oral
Value LD50 or LC50 with confidence limits	LD50 = 2220 (191 o-2600) mg/kg.
Number of deaths at each dose level	N G
Remarks for Results	The LD50 was reported to be 2220 mg/kg. Depression, diarrhea and scrawny appearance were noted.
Conclusion Remarks	The LD50 was reported to be 2220 (1910-2600) mg/kg.

Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal Food Cosmetic Toxicology,
References	Jenner, P. M., Hagan, E.C., Taylor, J.M, Cook, E.L. and Fitzhugh, O.G. (1964). Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity. Food and Cosmetics Toxicology 2(3): 327-343.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-o
Method/guideline	Six rabbits were used at 3 different dose levels 1, 2 & 3 g/kg. Chemical was applied to clipped area and was occluded for 24 hrs and the animals were observed for 7 days.
Test Type	Acute Dermal Toxicity test
GLP	**NG**
Year	**1971**
Species/Strain	Rabbits
Sex	Female
# of animals per sex per dose	2
Route of administration	Dermal
Remarks for Test Conditions	Highest dose was limited by the area available for treatment as well as by the chemical available.
Value LD50 or LC50 with confidence limits	The dermal lethal dose of the test substance was reported to be greater than 3 glkg.
Number of deaths at each dose level	No animals died at any dose level tested.
Remarks for Results	Moderate erythema was seen. Occasional sloughing was seen but this was in large part due to damage caused by the removal of the tape from the skin.
Conclusion Remarks	The dermal lethal dose of the test substance was reported to greater than 3 g/kg. Dermal LD50>3000 mg/kg bw.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Moreno O.M. (1971) Acute toxicity studies in rats, mice, rabbits and guinea pigs. Unpublished report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Acute dermal toxicity was determined in rabbits.
Test Type	Acute Dermal Toxicity
GLP	**NG**

Year	1977
Species/Strain	Rabbits
Sex	Not reported
# of animals per sex per dose	10
Vehicle	Not reported
Route of administration	Dermal
Value LD50 or LC50 with confidence limits	The dermal LD50 value for Lilial was calculated to be greater than 5 g/kg.
Number of deaths at each dose level	No death occurred
Remarks for Results	Mild redness was seen in 4 animals; moderate redness in 6 animals, mild edema in 7 animals and moderate edema in 3 animals.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Conclusion Remarks	The dermal LD50 value for Lilial was calculated to be greater than 5000 mg/kg.
References	Moreno 0. M. (1977b). Acute Oral toxicity in Rats. Dermal Toxicity in Rabbits. Unpublished. Report to RIFM.

Substance Name	alpha-Hexylcinnamaldehyde, light brown liquid with aromatic odor
CAS No.	101-86-O
Method/guideline	5 Sprague-Dawley rats per sex per dose received a single 4 hr exposure to aerosol containing test substance. Animals were observed for 14 days for body weight changes, mortality, clinical signs, gross and histopathological changes.
Test Type	Acute Inhalation toxicity
GLP	**NG**
Year	1980
Species/Strain	Sprague-Dawley rats
Sex	Male and Female
# of animals per sex per dose	**5**
Route of administration	Inhalation
Remarks for Test Conditions	The nominal chamber concentration, calculated from airflow and quantity of test article consumed was 5.00 mg/L. The mean value for the measured concentration was 2.12 mg/L in the chamber.
Value LD50 or LC50 with confidence limits	LC50> 5 mg/L
Number of deaths at each dose level	No deaths were reported

Remarks for Results	Enlarged bronical lymph nodes sometimes accompanied by pulmonary congestion, multiple grey-green pinpoint foci in the lungs, minimal loss of body weight on the days immediately following treatment.
Conclusion Remarks	The acute median lethal concentration was calculated to be greater than 5.00 mg/L expressed in terms of nominal concentration.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Breckenridge C. (1980). The acute toxicity of inhaled hexyl cinnamic aldehyde in the albino rats. Unpublished. Report to RIFM.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde, clear liquid.
CAS No.	80-54-6
Method/guideline	Test substance was applied at a dose of 5 ml/kg to the shaved skin of three rabbits of each sex and occluded for 24 h after which the rabbits were observed for 14 days for overt toxic signs and mortality.
Test Type	Acute Dermal Toxicity
GLP	**Yes**
Year	**1979**
Species/Strain	Albino New Zealand rabbits
Sex	Male and Female
# of animals per sex per dose	3
Route of administration	Dermal
Remarks for Test Conditions	
Value LD50 or LC50 with confidence limits	Dermal LD50 > 5 ml/kg
Number of deaths at each dose level	There were no deaths.
Remarks for Results	Treatment caused moderate erythema and thickened, wrinkled skin in all test animals, persisting through Day 9. Subcapsular (agonal) hemorrhages of the kidneys were found at necropsy in most of the test animals.
Conclusion Remarks	The acute dermal LD50 for the test substance was reported to be greater than 5 ml/kg. Acute dermal LD50>5250 mg/kg bw.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	Slepetys (1979). Cosmopolitan Safety Evaluation Unpublished Report. FEMA 15027.

Substance Name	alpha-Amylcinnamaldehyde

CAS No.	122-40-7
Method/guideline	Acute dermal toxicity was determined in rabbits.
Test Type	Acute Dermal Toxicity
GLP	N G
Year	1973
Species/Strain	Rabbits
Sex	Not reported
# of animals per sex per dose	4
Vehicle	Not reported
Route of administration	Dermal
Value LD50 or LC50 with confidence limits	The dermal LD50 value for alpha-amylcinnamaldehyde was calculated to be greater than 2000 mg/kg.
Number of deaths at each dose level	No death occurred
Remarks for Results	The was no evidence of toxicity at 2000 mg/kg bw
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Conclusion Remarks	The dermal LD50 value for alpha-amylcinnamaldehyde was calculated to be greater than 2000 mg/kg.
References	Moreno 0. M. (1973). Acute Oral toxicity in Rats. Dermal Toxicity in Rabbits. Unpublished. Report to RIFM.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	LD50 was computed by method of Litchfield & Wilcoxon (1949).
Test Type	Acute Oral LD50
GLP	Not reported
Year	**1964**
Species/Strain	Rst/Osborne-Mendel
Sex	Male and Female
# of animals per sex per dose	**5**
Vehicle	None
Route of administration	Oral
Value LD50 or LC50 with confidence limits	LD50 = 3730 (95% CI, 3190-4370) mg/kg. Slope function with 95% confidence interval=1.4 (1.2-1.6)

Number of deaths at each dose level	**NG**
Remarks for Results	The LD50 was reported to be 3730 mg/kg. Depression, porphyrin-like deposit around eyes and nose.
Conclusion Remarks	The LD50 was reported to be 3730 (31904370) mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal Food Cosmetic Toxicology,
References	Jenner, P. M., Hagan, E.C., Taylor, J.M, Cook, E.L. and Fitzhugh, O.G. (1964). Food Flavorings and Compounds of Related Structure I. Acute Oral Toxicity. Food and Cosmetics Toxicology 2(3): 327-343.

4.2 In Vitro Genotoxicity

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Cinnamaldehyde was tested for its antimutagenic effect on mitomycin C pretreated cells.
Test Type	Sister Chromatid Exchange
System of Testing	Chinese Hamster ovary cell
GLP	N G
Year	1987
Species/Strain	Chinese Hamster Ovary cells
Doses/Concentration	O-20 uM
Statistical Methods	N G
Remarks for Test Conditions	Chinese hamster ovary cells were treated in fresh medium containing the mutagen for 22 h. After treatment, cells were washed & incubated with cinnamaldehyde for 22 h. BudR at 20 uM was added. Mitotic cells were collected by the addition of colchicine.
Results	No increase in the frequencies of Sister Chromatid Exchange was observed after cells were treated with cinnamaldehyde alone. However, pretreatment of cells with mitomycin C resulted in increase in the frequency.
Cytotoxic concentration	N G
Genotoxic effects	None
Statistical results	N G
Conclusion Remarks	No evidence of mutagenicity by itself but increased the mutagenicity of mitomycin C.

	mutagenicity of mitomycin C.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Sasaki, Y.F., Imanishi, H., Ohta, T. and Shirasu, Y. (1987), Effects of antimutagenic flavourings on SCEs induced by chemical mutagens in cultured Chinese hamster cells. Mutation Research 189: 313-318.

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Method/guideline	Ames
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	NG
Year	1980
Species/Strain	Salmonella typhimurium/TA100
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats
Doses/Concentration	0.1, 0.2, 0.3 0.5, 1.2, 3 & 5 umoles/plate (13.2 to 320 ug/plate)
Statistical Methods	NG
Results	No mutagenic effects. Cinnamaldehyde and *alpha*-methylcinnamaldehyde were non-mutagenic for Salmonella typhimurium TAIOO both in the presence or absence of aroclor 1254 induced rat liver S9 mix.
Cytotoxic concentration	NG
Genotoxic effects	None
Statistical results	NG
Remarks for Results	Chloro or bromo substitution in the alpha-carbon position of cinnamaldehyde leads to the derivatives that are strongly mutagenic in Salmonella Typhimurium TAIOO.
Conclusion Remarks	No mutagenic activity
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Neudecker, T., Ohrlein, K, Eder, E and Henschler, D. (1983). Effect of Methyl and Halogen Substitutions in the alpha C position on the Mutagenicity of Cinnamaldehyde. Mutation Research 110: I-8.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Salmonella typhimurium strains TA97a, TA100, TA102 & TA104 in the presence and absence of aroclor-induced liver S9s from F344 rats & B6C3F1 mice.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	No
Year	1998
Species/Strain	Salmonella typhimurium/TA97a, TAIOO, TA102 and TA104
Metabolic Activation	With and without mice liver microsome fraction S9 from Aroclo induced rats and mice.
Doses/Concentration	25, 50, 100, 200 and 300 ug/plate
Statistical Methods	Dunnett's t-test and Wahrendorf ranking and linear regression.
Remarks for Test Conditions	Positive control: 2-aminoanthracene.
Results	frans-Cinnamaldehyde exhibited a weak mutagenic response in TAIOO with mouse liver S9 mix.
Cytotoxic concentration	NG
Genotoxic effects	Weak mutagenic response
Statistical results	NG
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Dillon, D., Combes, R. and Zeiger, E. (1998). The Effectiveness of Salmonella Strains TAIOO, TA102 and TA104 for Detecting Mutagenicity of Some Aldehydes and Peroxides. Mutagenesis 13(1):19-26.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The mutagenicity test was conducted in the Salmonella/microsome mutagenicity assay on plates according to the method of Ames with the Salmonella typhimurium TA98 and TA100.
Test Type	Reverse Mutation
System of Testing	Bacterial

GLP	NG
Year	1982
Species/Strain	Salmonella typhimurium TA 98, TA 100
Metabolic Activation	Rat-liver microsome (S9) was prepared from Sprague-Dawley rats treated with Aroclor 1254
Doses/Concentration	0.05 to 500 ug/plate.
Statistical Methods	NG
Remarks for Test Conditions	Diluted in DMSO
Results	Negative
Cytotoxic concentration	Not reported
Genotoxic effects	Negative
Statistical results	NG
Conclusion Remarks	No mutagenic effects
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., and Urasawa, S. (1982). Genotoxcity of Flavoring Agents. Mutation Research 105:387-392.

Substance Name	Cinnamaldehyde
CAS No.	**104-55-2**
Method/guideline	Exponentially growing Chinesehamster B241 were exposed to the test substance for 24 hr and then incubated for another 24 hrs without the test chemical followed by treatment with colchicine.
Test Type	Chromosomal Aberration Test
System of Testing	Non Bacterial
GLP	NG
Year	1982
Species/Strain	Chinese hamster cell line B241
Metabolic Activation	Rat-liver microsome (S9) was prepared from Sprague-Dawley rats treated with Aroclor 1254. Rat-liver microsome (S9) was prepared from Sprague-Dawley rats treated with Aroclor 1254.
Doses/Concentration	Several doses up to IO nM.
Statistical Methods	Chi-Square test

Remarks for Test Conditions	The test chemical was dissolved in DMSO at a concentration of 50 mM and then was diluted with the medium. Control cells were treated with a medium containing DMSO equal to the test solution.
Results	trans-Cinnamaldehyde exhibited high potential for inducing aberrations. The total frequency of the aberrations indicated a dosedependent increase at a certain dose range. DMSO did not affect the frequency or the type of spontaneous aberrations
Cytotoxic concentration	Not reported
Genotoxic effects	Chromosomal aberrations
Statistical results	NG
Remarks for Results	Chromatid break, chromosome break, chromatid exchange, ring or dicentric chromosomes, fragmentation, translocation and pulverization were observed.
Conclusion Remarks	Severe chromosome aberrations were observed in the cells treated with Cinnamaldehyde,
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., and Urasawa, S. (1982). Genotoxcity of Flavoring Agents. Mutation Research 105:387-392.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The mutagenicity assay with Salmonella typhimurium was conducted as described by Ames et al with tester strain TA100 and TA98. S9 was prepared from the PC&treated male Sprague-Dawley rats.
Test Type	Reverse Mutation assay
System of Testing	Bacterial
GLP	NG
Year	1982
Species/Strain	Salmonella typhimurium/TA100, TA98, TA1535, TA1537 and TA1538.
Metabolic Activation	S9 fraction was prepared from the PCB-treated male Sprague-Dawley rats
Doses/Concentration	60, 120, 300 and 600 ug/plate.
Statistical Methods	None performed
Remarks for Test Conditions	Histidine-independent colonies were scored after incubation at 37C for 48-72 h.
Results	No significant increase in revertant number with Salmonella strains in the presence or absence of S9 fraction.
Cytotoxic concentration	600 uglplate

Genotoxic effects	Negative
Statistical results	N G
Conclusion Remarks	Cinnamaldehyde was not found to be mutagenic under the test conditions
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Sekizawa, J. and Shibamoto, T. (1982). Genotoxicity of Safrole-Related Chemicals in Microbial Test Systems. Mutation Research 101: 127-l 40.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The mutagenicity assay with E. coli WP2uorA trp- was performed according to the method described by Green and Murial (1976).
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	N G
Year	1982
Species/Strain	E. coli/WP2 uorA trp-
Metabolic Activation	S9 fraction was prepared from the PCB-treated male Sprague-Dawley rats
Doses/Concentration	60, 120, 300 and 600 ug/plate.
Statistical Methods	N G
Remarks for Test Conditions	After 48-72 h incubation at 37 °C, revertant colonies were counted.
Results	No mutagenic effects.
Cytotoxic concentration	600 ug/plate
Genotoxic effects	None
Statistical results	N G
Conclusion Remarks	No evidence of mutagenicity was seen under the test condition.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Sekizawa, J. and Shibamoto, T. (1982). Genotoxicity of Safrole-Related Chemicals in Microbial Test Systems. Mutation Research 101: 127-140.

Substance Name	Cinnamaldehyde
CAS No.	*104-55-2*
Method/guideline	The DNA-repair test with Bacillus subtilis was performed as described by Kada et al. (1980).
Test Type	DNA-Repair test
System of Testing	Bacterial
GLP	N G
Year	1986
Species/Strain	Bacillus subtilis/H17 Rec+ or M45 Rec-
Metabolic Activation	S9 fraction was prepared from the PCB-treated male Sprague-Dawley rats.
Doses/Concentration	0.2 mg/disk
Statistical Methods	N G
Results	No mutagenic effects in the absence of S9 fraction. DNA-repair tests with S9 were not successful.
Genotoxic effects	None
Statistical results	N G
Conclusion Remarks	No evidence of mutagenicity was detected under the test conditions.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Sekizawa, J. and Shibamoto, T. (1982). Genotoxicity of Safrole-Related Chemicals in Microbial Test Systems. Mutation Research 101: 127-140.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	*122-40-7*
Method/guideline	Ames test was performed on five tester strains of Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	**NG**
Year	*1983*
Species/Strain	Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.

Metabolic Activation	S-9 liver fraction was prepared from Aroclor-pretreated rats (Aroclor 1254, 500 mg/kg, ip).
Doses/Concentration	up to 3600 ug/plate
Statistical Methods	Statistical significance was determined according to the methods of Kastenbaum and Bowman (1970).
Remarks for Test Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo[a]pyrene.
Results	No mutagenic activity was detected with any of the Salmonella strains tested.
Cytotoxic concentration	N G
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity was detected with any of the Salmonella strains tested.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Wild, D., King, M.-T., Gocke, E. and Eckhardt. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxicol. 21(6): 707-719.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The antimutagenic effect of Cinnamaldehyde (CA) on the induction of HGPRT- mutants by methyl methanesulfonate (MMS), N-nitroso-N-methylurea (MNU), ethyl methanesulfonate (EMS) and UV light was investigated in the Chinese hamster V79 cell line.
Test Type	HGPRT- Mutants
System of Testing	Cell line
GLP	**NG**
Year	**1994**
Species/Strain	Chinese hamster/V79 cell line
Metabolic Activation	None
Doses/Concentration	50 or 100 mM.
Statistical Methods	Student t-test
Remarks for Test Conditions	Cells were seeded & then treated with UV light (12 J/m3) or MMS (2 mM), EMS (30 mM) or MNU (1 mM) for 1 h. Then the cells were washed 2X & the incubation was continued with fresh medium containing CA (0, 50 or 100 mM) for 2 or 4 h. Cell was washed, trypsinized & were seeded. The survival was measured by seeding 10E2 cells in a fresh medium. Mutation frequency was calculated as mutants/10E6 viable cells.

Results	No mutagenic effect of CA; did not modify the mutation frequency when given to cells simultaneously with chemical mutagens MNU, EMS. MMS or UV; increased the cytotoxicity of MMS but not of MNU & EMS
Cytotoxic concentration	150 uM
Genotoxic effects	None
Conclusion Remarks	Cinnamaldehyde inhibits some cellular function(s) promoting the repair of a variety of different cytotoxic lesions. At the same time, stimulation by Cinnamaldehyde of an error-free DNA repair mechanism acting on methyl methanesulfonate induced mutagenic damage was indicated.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Fiorio, R. and Bronzetti, G.(1994). Effects of Cinnamaldehyde on Survival and Formation of HGPRT- Mutants in V79 Cells Treated with Methyl Methanesulfonate, N-Nitroso-N-Methylurea, Ethyl Methanesulfonate and UV Light. Mutation Research 324: 51-57.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The chemical was tested in Strains of Salmonella using a liquid preincubation procedure.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	N G
Year	1985
Species/Strain	Salmonella typhimurium/TA104 & TA102
Metabolic Activation	None
Doses/Concentration	Tested up to the toxic concentration. (Unspecified)
Remarks for Test Conditions	Use of two strains, TA104 and TA102 is described.
Results	Negative
Genotoxic effects	No mutagenic activity was repotted.
Conclusion Remarks	No mutagenic activity of Cinnamaldehyde was detected by the use of two new base substitution strains TA104 and TA102.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Marnett, L.J., Hurd, H.K., Hollstein, M.C., Levin, D.E., esterbauer, H., and Ames, B.N. (1985). Naturally Occurring

Carbonyl Compounds are Mutagens in Salmonella Tester Strain TA104. Mutation Research 148: 25-34.

Substance Name	*trans*-Cinnamaldehyde (>95% pure)
CAS No.	104-55-2
Method/guideline	Cinnamaldehyde was tested for mutagenicity in five strains of Salmonella typhimurium both in the presence or absence of S-9 mix. Both the plate incorporation tests and the liquid preincubation assay were performed.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	NG
Year	1980
Species/Strain	Salmonella typhimurium/TA1535, TA1537, TA1538, TA98 and TAIOO
Metabolic Activation	Rat or hamster liver homogenates from animals stimulated with Aroclor 1254 (500 mg/kg 5 days).
Doses/Concentration	I- 500ug/plate
Results	Negative
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity of cinnamaldehyde was detected either by the plate incorporation test or by the liquid preincubation assay in the presence or absence of rat or hamster S-9 fraction.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Lijinsky, W. and Andrews A.W. (1980). Mutagenicity of Vinyl Compounds in Salmonella Typhimurium. Teratogenesis, Carcinogenesis and Mutagenesis 1: 259-269.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Reverse mutation assay using Salmonella typhimurium strains TA92, TA1535, TAIOO, TA1537, TA94 and TA98 was carried out according to the method of Ames.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	**NG**
Year	**1984**

Species/Strain	Salmonella typhimurium/TA92, TA1535, TA100, TA1537, TA94 and TA98
Metabolic Activation	Liver microsome fraction (S-9) prepared from the liver of Fischer rats pretreated 5 days before with polychlorinated biphenyls (500 mg/kg, ip).
Remarks for Test Conditions	Solvent used DMSO
Results	Cinnamic aldehyde induced 222 revertants (146 in control) at 0.5 mg/plate and 318 revertants (139 in control) at 0.1 mg/plate in TAIOO with and without S-9 mix, respectively.
Genotoxic effects	Positive
Conclusion Remarks	Cinnamic aldehyde was reported to be mutagenic in Salmonella typhimurium strain TA100 in the presence and absence of S-9 mix.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Ishidate, M., Sofuni, T., Yoshikawa, K., Hauashi, M., Nohmi, T., Sawada, M. and Matsuoka. (1984). Primary Mutagenicity Screening of Food Additives Currently Used in Japan. Fd. Chem. Toxic. 22(8) 623-636.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Ames test was performed on two tester strains of Salmonella typhimurium TA 97and TA 102.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	N G
Year	1987
Species/Strain	Salmonella typhimurium/TA97 and TA 102
Metabolic Activation	S-9 liver fraction was prepared from Aroclor-pretreated rats (Aroclor 1254, 500 mg/kg, ip).
Doses/Concentration	I-I 000 ug/plate
Statistical Methods	Kruskal-Wallis test
Remarks for Test Conditions	Preincubation method using positive controls of 9-AA (20 ug/plate) for TA 97 with activation and 5 ug/plate without activation (S-9). Positive control for TA 102 was MMC (0.5 ug/plate) without activation and 9-AA (5 ug/plate) without activation.
Results	No mutagenic effects with or without S9 activation
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity was detected with any of the Salmonella strains tested.

Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Fujita H. and Sasaki M (1987) Mutagenicity Test of food additives with Salmonella Typhirium TA 97 and TA102. Annals of Tokyo Metr. Research Laboratory P.H. 38:423-430.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	**10** l-86-0
Method/guideline	Ames test was performed on five tester strains of Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	N G
Year	1983
Species/Strain	Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.
Metabolic Activation	S-9 liver fraction was prepared from Aroclor-pretreated rats (Aroclor 1254, 500 mg/kg, ip).
Doses/Concentration	up to 3600 ug/plate
Statistical Methods	Statistical significance was determined according to the methods of Kastenbaum and Bowman (1970).
Remarks for lest Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo[a]pyrene.
Results	No mutagenic activity was detected with any of the Salmonella strains tested.
Cytotoxic concentration	N G
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity was detected with any of the Salmonella strains tested.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Wild D., King, M.T., Gocke, E. and Eckhardt. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus tests Food and Chemical Toxicology 21(6), 707-719.

Substance Name	*p*-tert-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Method/guideline	Ames test was performed on five tester strains of Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 1538, TA 98.

Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	**NG**
Year	**1984**
Species/Strain	Salmonella typhimurium/TA 1535, TA 100, TA 1537, TA 1538, TA 98
Metabolic Activation	4 or 10% Aroclor-induced S9 fraction prepared from the PCB-treated male Sprague-Dawley rats
Doses/Concentration	0.0078 to 0.125 ul/plate
Statistical Methods	**NG**
Remarks for Test Conditions	Solvent, Ethanol. Plate incorporation method using positive controls of 2-acetylaminofluorene (2ug/plate) for TA 98 and TA1538, mitomycin C (1 uglplate) for TA102, so with activation and 5 ug/plate without activation (S-9). Positive control.
Results	No mutagenic activity was detected with any of the Salmonella strains tested with or without S9 activation.
Cytotoxic concentration	NG
Genotoxic effects	None
Conclusion Remarks	No mutagenic activity was detected with any of the Salmonella strains tested.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Basic data given comparable to guidelines/standards.
References	Givaudan-Roure (1984) Mutagenicity evaluation of *p-t-butyl-alpha-methylhydrocinnamaldehyde* in the Salmonella/mammalian plate incorporation assay. Unpublished Report to RIFM.

Substance Name	p-tert-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	*122-40-7*
Method/guideline	Ames test was performed on five tester strains of Salmonella typhimurium (TA 1535, TA 100, TA 1537, TA 98).
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	**NG**
Year	1991
Species/Strain	Salmonella typhimurium/TA 1535, TA 100, TA 1537, TA 98.
Metabolic Activation	S9 fraction was prepared from the PCB-treated male Sprague-Dawley rats.
Doses/Concentration	2.5 to 750 uglplate without activation and 250 uglplate with activation.

Statistical Methods	**NG**
Remarks for Test Conditions	Solvent, DMSO.
Results	No mutagenic activity was detected with any of the Salmonella strains tested with or without S9 activation.
Cytotoxic concentration	667 ug/plate with (+S9), 333 ug/plate (-S9)
Genotoxic effects	None
Statistical results	NG
Conclusion Remarks	No mutagenic activity
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Basic data given comparable to guidelines/standards.
References	Wagner V.O., and Twarszik, S. C. (1999) Bacterial reverse mutation assay of p-t-butyl-alpha-methyldihydrocinnamic aldehyde. Unpublished journal.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Chromosomal aberration test was carried out using a Chinese hamster fibroblast cell line, CHL. The cells were exposed to 3 different doses for 24 and 48 hours. No metabolic activation system was applied.
Test Type	Chromosomal aberration test
System of Testing	Chinese hamster fibroblast cell line CHL.
GLP	NG
Year	1984
Species/Strain	Chinese hamster fibroblast cell line CHL.
Metabolic Activation	None
Doses/Concentration	Max. dose = 0.015 mg/ml
Remarks for Test Conditions	For quantitative evaluation of the clastogenic potential, the D20 was calculated, which is the dose (mg/ml) at which structural aberrations (including gaps) were detected in 20% of the metaphases observed. In addition, the TR value was calculated, which indicates the frequency of cells with exchange-type aberrations per unit dose (mg/ml). TR values are relatively high for chemicals that show carcinogenic potential in animals.
Results	Cinnamic aldehyde was positive in chromosomal aberration test. TR value was 2133 and D20 = 0.01. It was also positive at 0.01 mg/ml at 24 h (20.0%, total incidence of cells with aberrations) and at 48 hr (15%, total incidence of cells with aberrations). The results were considered positive if the total

	incidence of ceils with aberrations was 10.0% or more.
Genotoxic effects	Positive
Conclusion Remarks	Cinnamic aldehyde was shown to be positive in chromosomal aberration test.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Ishidate, M., Sofuni, T., Yoshikawa, K., Hauashi, M., Nohmi, T., Sawada, M. and Matsuoka. (1984). Primary Mutagenicity Screening of Food Additives Currently Used in Japan. Fd. Chem. Toxic. 22(8) 623-636.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The test chemical was screened for mutagenic activity using Salmonella typhimurium strains TA97, TA98, and TAIOO with and without S9 metabolic activation using prolonged, non-standard preincubation time of up to 120 minutes.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	N G
Year	1995
Species/Strain	Salmonella typhimurium Strain TA97, TA98 and TAIOO
Metabolic Activation	S9 fraction used but source not specified
Results	No mutagenic activity was detected
Genotoxic effects	None
Statistical results	N G
Data Qualities Reliabilities	Data appears to be reliable.
Remarks for Data Reliability	Reliability code 2. Reliable with restrictions.
References	Azizian, A. and Blevins, R.D. (1995). Mutagenicity and Antimutagenicity Testing of Six Chemicals Associated with the Pungent Properties of Specific Spices as Revealed by the Ames Salmonella/Microsomal Assay, Arch. Environ. Contam. Toxicol. 28: 248-258.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2

Method/guideline	The genotoxicity of cinnamaldehyde was studied by a bacterial mutation test in the Salmonella/microsome system with and without rat-liver microsome as the metabolic activation system.
Test Type	Reverse Mutation
System of Testing	Bacterial
GLP	NG
Year	1982
Species/Strain	Salmonella typhimurium Strain TA98 and TAIOO
Metabolic Activation	Rat-liver microsomes
Doses/Concentration	0.05 to 500 ug/plate
Results	Test substance did not induce a number of revertants that was over half of the number of spontaneous revertants of TA98 or TAIOO either with or without S9 mix. Considerable mutagenic activity was seen in positive standard mutagens.
Genotoxic effects	None
Conclusion Remarks	Cinnamaldehyde did not induce a number of revertants that was over half of the number of spontaneous revertants of TA98 or TAIOO either with or without S9 mix.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was published in a peer review journal.
References	Kasamaki, A., Takahashi, H, Niwa, J., Fujita, T. and Urasawa, S. (1982). Genotoxicity of Flavoring Agents. Mutation Research 105: 387-392.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Cinnamaldehyde was tested for genotoxicity using CH cell line B241 in culture stages between the 5th and 8th passages.
Test Type	Chromosomal aberration
System of Testing	Cell line
GLP	**NG**
Year	**1982**
Species/Strain	Chinese Hamster cell line 8241
Metabolic Activation	Rat liver microsome from Sprague-Dawley rats treated with Aroclor 1254

Remarks for Test Conditions	One day after seeding, exponentially growing cells were exposed to the test chemical for 24 hrs, then incubated for another 24 hrs without chemical followed by treatment with colchicine (1 X IO-7M) for 2-3 hrs. Chromosome samples were prepared by the Giemsa staining method. Control cell cultures were treated with a medium containing DMSO equal in its concentration to the test solution of test chemical. The percentage of chromosome aberration was computed by scoring about 200 metaphase spreads, each containing 20-26 chromosomes.
Results	Cinnamaldehyde induced severe chromosome aberration in the treated CH cells suggesting a potential genotoxicity.
Genotoxic effects	Induced severe chromosome aberration
Remarks for Results	Various types of aberrations were observed in the treated cells, such as severe chromatid break, chromosome break, chromatid exchange, ring or dicentric chromosomes, fragmentation, translocation and pulverization.
Conclusion Remarks	Cinnamaldehyde induced severe chromosome aberration in the treated CH cells suggesting a potential genotoxicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer review journal.
References	Kasamaki, A., Takahashi, H, Niwa, J., Fujita, T. and Urasawa, S. (1982). Genotoxicity of Flavoring Agents. Mutation Research 105: 387-392.

4.3 In Vivo Genotoxicity

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Mouse bone marrow micronucleus assay.
Test Type	Micronucleus Test
GLP	**NG**
Year	1984
Species/Strain	Mice/ddY
Sex	Male
Route of administration	Intraperitoneal
Doses/concentrations	125250,500 & 1000 mg/kg
Exposure period	18, 24, 30, 48, or 72 hrs

Remarks for Test Condition	Mice received one of the 4 different doses of the test material by IP and were killed after a time interval of 18, 24, 30, 48 or 72 hr following injection. Femoral marrow cells were smeared, fixed and stained. 100 polychromatic erythrocytes were scored and the number of micronucleated polychromatic erythrocytes were recorded.
Genotoxic effects	Not genotoxic
Remarks for Results	Micronucleated polychromatic erythrocytes did not increase in any dose or any sampling time. At 500 mg/kg more than 1 animal died; at 1000 mglkg all animals died.
Conclusion Remarks	No evidence of genotoxicity.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Hayashi, M., Sofuni, T and Ishidate, M. (1984). A Pilot Experiment for the Micronucleus Test. The multi-sampling at multi-dose levels method. Mutation Research 141: 165-169.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Methodlguideline	Mouse
Test Type	Micronucleus test
GLP	NG
Year	1990
Species/Strain	ddY mice
Sex	Male
Route of administration	Oral
Doses/concentrations	250, 313, or 500 mglkg bw
Exposure period	Single dose
Remarks for Test Condition	Male ddY mice were irradiated with Xray at 200 rad. After irradiation cinnamaldehyde was administered orally at 250, 313 or 500 mglkg. In a time course study 500 mglkg was given to mice immediately after the irradiation and the bone-marrow cells were sampled periodically. The micronucleus assay was performed according to the method described by Schmid 1976.
Genotoxic effects	Not genotoxic
Appropriate statistical evaluations?	Student t-test
Remarks for Results	A dose-dependent decrease in micronucleated polychromatic erythrocytes. At 500 mglkg, there was 58% decrease in MNPCE. The test material did not increase the frequency of polychromatic erythrocytes, indicating that observed reduction

	of MNPCE was not a reflection of toxic effect of cinnamaldehyde on the bone-marrow.
Conclusion Remarks	Cinnamaldehyde reduced the frequency if Xray induced micronuclei with toxicity of the test chemical to the bone marrow.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Sakasi, Y. F., Ohta, T., Imanishi, H, Watanabe, M., Matsumoto, K., Kato, T., and Shirasu, Y. (1990). Suppressing Effects of Vanilin, Cinnamaldehyde, and Anisaldehyde on Chromosome aberrations induced by Xrays in mice. Mutation Research 243: 299-302.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	DNA Fragmentation/Alkaline Elution Assay
Test Type	DNA Fragmentation/Alkaline Elution Assay
GLP	N G
Year	1994
Species/Strain	Sprague-Dawley rats
Sec	Male
Route of administration	Oral
Doses/concentrations	1100 mg/kg
Exposure period	Single dose. Animals killed after 3 hrs.
Remarks for Test Condition	Male albino Sprague-Dawley rats were given by gastric intubation a single dose (1100 mg/kg) of Cinnamaldehyde in carboxymethylcellulose. Rats were killed 3 hrs after treatment. DNA fragmentation (Single Strand break &/or Alkali-liable sites) was evaluated by the Alkaline Elution Technique.
Genotoxic effects	None
Remarks for Results	Cinnamaldehyde did not induce DNA fragmentation in liver and gastric mucosa as evaluated by the alkaline elution technique.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mereto, E., Brambilla-Campart, G., Ghia, M., Martelli, A., and Brambilla, G. (1994). Cinnamaldehyde-induced micronuclei in rodent liver. Mutation Research 322: 1-8.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Cinnamaldehyde induced micronuclei in rodent liver was investigated.
Test Type	Micronuclei Assay
GLP	NG
Year	NG
Species/Strain	Male Albino Sprague-Dawley rats
Sex	Male
Route of administration	Oral
Doses/concentrations	550, 1100 or 1650 mg/kg.
Exposure period	Single oral dose
Remarks for Test Condition	Animals were subjected a 2/3 hepatectomy 20 hrs before dosing in order to determine the clastogenic effect on hepatocytes and were killed 48 hrs after cinnamaldehyde administration. The frequency of micronucleated polychromatic erythrocytes was evaluated in marrow, hepatocytes and gastric mucosa.
Genotoxic effects	Not genotoxic
Remarks for Results	No increase in the frequency of MNPCE in bone marrow 48 hrs after administration of cinnamaldehyde; it induced a dose dependent clastogenic effect in the liver; significantly higher incidence of total nuclear anomalies but not of micronucleated cells in forestomach mucosa
Conclusion Remarks	High doses of cinnamaldehyde may produce a clastogenic effect.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mereto, E., Brambilla-Campart, G., Ghia, M., Martelli, A., and Brambilla, G. (1994). Cinnamaldehyde-induced micronuclei in rodent liver. Mutation Research 322: I-8.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Cinnamaldehyde induced micronuclei in rodent liver was investigated.
Test Type	Micronuclei Assay
GLP	**NG**
Year	1994

Species/Strain	Male Albino Swiss mice
Sex	Male
Route of administration	Oral
Doses/concentrations	850, 1200 or 2550 mg/kg
Exposure period	Single oral dose
Remarks for Test Condition	Animals were subjected to a 2/3 hepatectomy 20 hrs before dosing in order to determine the clastogenic effect on hepatocytes and were killed 48 hrs after cinnamaldehyde administration. The frequency of micronucleated polychromatic erythrocytes was evaluated in marrow, hepatocytes and gastric mucosa.
Genotoxic effects	Not genotoxic
Remarks for Results	No increase in the frequency of MNPCE in bone marrow 48 hrs after administration of cinnamaldehyde; it induced a dose dependent clastogenic effect in the liver.
Conclusion Remarks	High doses of cinnamaldehyde may produce a clastogenic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mereto, E., Brambilla-Campart, G., Ghia, M., Martelli, A., and Brambilla, G. (1994). Cinnamaldehyde-induced micronuclei in rodent liver. Mutation Research 322: 1-8.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Solt-Farber Assay System
Test Type	Solt-Farber Assay System
GLP	N G
Year	1994
Species/Strain	Male Sprague-Dawley rat
Sex	Male
Route of administration	Gavage
Doses/concentrations	500 mglkg
Remarks for Test Condition	Three groups of rats were initiated with NDEA (200 mg/kg ip). Two weeks later, Group 1: received 14 successive day of cinnamaldehyde; Group 2: rats were fed diet containing 0.02% 2 AAF (+ve control); Group 3: no treatment (-ve control). On day 7, all rats were hepatectomized. On day 28 all rats were killed and liver removed.

Genotoxic effects	Not genotoxic
Remarks for Results	Rats initiated with NDEA, administration of cinnamaldehyde for 14 days produce significant increase in average diameter & area of gamma-glutamyltraspeptidase positive foci that might be considered as indication of a potential promoting activity.
Conclusion Remarks	The high doses of cinnamaldehyde may possibly a produce promoting effect in the liver of previously initiated animals.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mereto, E., Brambilla-Campart, G., Ghia, M., Martelli, A., and Brambilla, G. (1994). Cinnamaldehyde-induced micronuclei in rodent liver. Mutation Research 322: l-8.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	DNA-Repair assay was carried out to examine the ability of the test chemical to induce unscheduled DNA synthesis (UDS) or S-phasesynthesis (SPS) in Fischer-344 rats. Animals were administered the test chemical by oral gavage as a single bolus
Test Type	DNA repair assay
GLP	N G
Year	1989
Species/Strain	Fischer-344 rats
Sex	Male
Route of administration	Oral
Doses/concentrations	UDS: - 50, 200, or 1000 mg/kg.
Remarks for Test Condition	Doses were selected based approximately on the oral LD50 value and was selected as 80%, 40% and 10% of the LD50. Two doses were selected for SPS studies and three doses were utilized for UDS studies. SPS was examined at 48 hr post treatment.
Remarks for Results	Cinnamaldehyde failed to induced UDS or SPS in rats at the doses tested.
Conclusion Remarks	Cinnamaldehyde failed to induce the UDS or SPS in rats.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mirsalis, J.C., Tyson, C.K., Steinmetz, K. L., Loh, E.K., Hamilton, CM., Bakke, J.P. and Spalding, J.W. (1989). Measurement of Unscheduled DNA Synthesis and S-Phase Synthesis in Rodent Hepatocytes Following In Vivo Treatment: Testing of 24 Compounds. Environmental and Molecular Mutagenesis 14: 155-164.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	DNA
Test Type	DNA repair assay
GLP	NG
Year	1989
Species/Strain	B6C3F1 mice
Sex	Male and Female
Route of administration	Oral
Doses/concentrations	UDS: 50, 200, or 1000 mg/kg.
Remarks for Test Condition	Doses selected based approximately on the oral LD50 value and selected as 80%, 40% and 10% of the LD50. Two doses were selected for SPS studies and three doses were utilized for UDS studies. SPS was examined at 48 hr post treatment.
Genotoxic effects	Not genotoxic
Remarks for Results	Cinnamaldehyde failed to induce UDS or SPS in mice at the doses tested.
Conclusion Remarks	Cinnamaldehyde failed to induce the UDS or SPS in mice.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Mirsalis, J.C., Tyson, C.K., Steinmetz, K. L., Loh, E.K., Hamilton, C.M., Bakke, J.P. and Spalding, J.W. (1989). Measurement of Unscheduled DNA Synthesis and S-Phase Synthesis in Rodent Hepatocytes Following In Vivo Treatment: Testing of 24 Compounds. Environmental and Molecular Mutagenesis 14: 155-164.

Substance Name	*p*-tert-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	**80-54-6**
Method/guideline	Micronucleus test
Test Type	Micronucleus test
GLP	**NG**
Year	**2000**
Species/Strain	ICR mice

Sex	Male and Female
Route of administration	Intraperitoneal
Doses/concentrations	150, 300, or 600 mglkg
Exposure period	Single intraperitoneal dose
Remarks for Test Condition	Mice received one of the 3 different doses of the test material by IP and were killed after a time intervals of 48 or 72 hr following injection. Femoral marrow cells were smeared, fixed and stained with May-Gruenwald-Giemsa. 2000 polychromatic erythrocytes were scored and the number of micronucleated polychromatic erythrocytes were recorded.
Genotoxic effects	A slight increase (9/1000), males at 600mg/kg
NOEL (C)/LOEL (C)	300 mglkg
Remarks for Results	The authors noted the response was not biologically significant since only one animal in the 600 mglkg level had 3MNPCE which is within the historical control range (O-7 MN/2000 PCE/animal. No significant increase and no doserelated increase was observed in any other group regardless of dose, sex, or collection time.
Conclusion Remarks	No evidence of genotoxicity
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
References	Gudi R. and Krsmanovic L. (2000) Mammalian erythrocyte micronucleus test of *para*-tert-butyl-*alpha*-methylhydrocinnamic aldehyde. Unpublished report.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	BASC test on Drosophila was performed as reported in Eckhardt, King, Gocke and Wild, 1980.
Test Type	BASC test
GLP	NG
Year	19983
Species/Strain	Insect, Drosophila melanogaster
Sex	Male and Female
Route of administration	Oral
Doses/concentrations	10 mM
Remarks for Test Condition	The test substance to be fed to the flies was prepared in 5% saccharose, with addition of 2% ethanol and 2% Tween 80. Ethyl nitrite was administered to Drosophila males in gaseous form. To do this flies were kept for 3 days in l-liter bottle containing small amount of medium, and ethyl nitrite was

	injected into the tightly closed bottles.
Genotoxic effects	None
NOEL (C)/LOEL (C)	10 mM
Remarks for Results	No mutagenic activity was demonstrated under the test conditions
Conclusion Remarks	No mutagenic activity was demonstrated under the test conditions
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
General Remarks	A significant increase in sex-linked recessive lethal mutations in single test but repeated tests did not confirm the mutagenic activity. This anomaly was ascribed to chance.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxic. 21(6): 707-719.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	122-40-7
Method/guideline	Micronucleus test. NMRI mice were treated once with the test material. The mice were killed and bone-marrow smear was prepared 30 hours after the treatment. The smears were stained according to the Schmid method & slides were scored.
Test Type	Micronucleus test
GLP	N G
Year	1983
Species/Strain	NMRI mice
Sex	Male and Female
Route of administration	Not given
Doses/concentrations	0, 405, 809, 1213 mg/kg
Effect on mitotic index or PCE/NCE ration by dose level and sex	Dose: 0 mg/kg = 2.7 mean MNPE/1000PE; 405mg/kg=1.3 mean MNPE/1000 PE; 809 mg/kg=3.0 MNPE/1000 PE; 1213 mg/kg=1.5 MNPE/1000 PE PE = Polychromatic erythrocytes; MNPE = Micronucleated Polychromatic Erythrocytes.
Genotoxic effects	None
NOEL (C)/LOEL (C)	1213 mg/kg
Remarks for Results	No mutagenic activity was detected under the test conditions.

Conclusion Remarks	No mutagenic activity was detected under the test conditions.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxic. 21(6): 707-719.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	BASC test on Drosophila was performed as reported in Eckhardt, King, Gocke and Wild, 1980.
Test Type	BASC test
GLP	N G
Year	19983
Species/Strain	Insect, Drosophila melanogaster
Sex	Male and Female
Route of administration	Oral
Doses/concentrations	10 mM
Remarks for Test Condition	The test substance to be fed to the flies was prepared in 5% saccharose, with addition of 2% ethanol and 2% Tween 80. Ethyl nitrite was administered to Drosophila males in gaseous form. To do this flies were kept for 3 days in l-liter bottle containing small amount of medium, and ethyl nitrite was injected into the tightly closed bottles,
Genotoxic effects	None
NOEL (C)/LOEL (C)	10 mM
Remarks for Results	No mutagenic activity was demonstrated under the test conditions. No of sex-linked lethals/chromosomes tested; Control: Brood I, 42/18.188; Brood II, 34117,734; Brood III, 50116,980 Test Material; Brood I, 1012426; Brood II, 212418; Brood III, 6/2405.
Conclusion Remarks	No mutagenic activity was demonstrated under the test conditions
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions,
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
General Remarks	A significant increase in sex-linked recessive lethal mutations in single test but repeated tests did not confirm the mutagenic activity. This anomaly was ascribed to chance.

References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxic. 21(6): 707-719.

Substance Name	*alpha*-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Micronucleus test. NMRI mice were treated once with the test material. The mice were killed and bone-marrow smear was prepared 30 hours after the treatment. The smears were stained according to the Schmid method & slides were scored.
Test Type	Micronucleus test
GLP	N G
Year	1983
Species/Strain	NMRI mice
Sex	Male and Female
Route of administration	Not given
Doses/concentrations	**0, 324, 540, 756** mg/kg
Effect on mitotic index or PCE/NCE ration by dose level and sex	Dose: 0 mg/kg = 1.0 mean MNPE/1000PE; 324mg/kg=2.1 mean MNPE/1000 PE; 540 mg/kg=1.8 MNPE/1000 PE; 756 mg/kg=2.4 MNPE/1000 PE PE = Polychromatic erythrocytes; MNPE = Micronucleated Polychromatic Erythrocytes.
Genotoxic effects	None
NOEL (C)/LOEL (C)	**756** mg/kg
Remarks for Results	No mutagenic activity was detected under the test conditions.
Conclusion Remarks	No mutagenic activity was detected under the test conditions.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983). Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxic. 21(6): 707-719.

4.4 Repeat Dose Toxicity

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Test Material was administered orally for 13 weeks to 3 groups of 6 beagle dogs by means of gelatin capsules. Six dogs were kept as controls and received the empty gelatin capsules.
GLP	Yes
Year	1990
Species/Strain	Beagle dogs
Sex	Male and Female
Route of administration	Oral
Doses/concentration	4.4, 22.3 or 44.6 mg/kg
Exposure	91 days
Frequency of treatment	Daily
Control Group and treatment	Yes
Post exposure observation period	NG
NOAEL (NOEL)	44.6 mg/kg
LOAEL (LOEL)	No adverse effects at highest dose
Actual dose received by dose level and sex	NG
Toxic response/effects by dose level	None
Statistical evaluations	DUNN test
Remarks for Results	No adverse effect with respect to the general state of health, the body weight development, the behavior of the dogs, hematological & clinical chemical parameters & opthalmoscopy, macroscopic, pathology & histological appearance of the organs and tissues examined were noted.
Conclusion Remarks	This study demonstrates a NOAEL in dogs of at least 44.6 mg/kg/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	Givaudan Roure (1990b). A toxicity study following oral administration of p-t-butyl alpha-methylhydrocinnamic aldehyde in dogs during a period of 13 weeks. Unpublished Report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Test material was orally administered at 200 mg/kg/day to 3 female beagle dogs by means of gelatine capsules for a period of 91 days. Incompatibility reactions, body weights & the group feed intake were recorded.
GLP	NG
Year	1990
Species/Strain	Beagle dogs
Sex	Female
Route of administration	Oral
Doses/concentration	200 mg/kg/day
Exposure	13 weeks
Control Group and treatment	Yes
Post exposure observation period	NG
Remarks	Blood chemistry tests & an autopsy were performed. Blood parameters measured: Aspattate aminotransferase, cholinesterase, cholesterol, alkaline phosphatase, *gamma*-glutamiltransferase.
NOAEL (NOEL)	200 mg/kg
Actual dose received by dose level and sex	NA
Toxic response/effects by dose level	None
Statistical evaluations	NG
Remarks for Results	The administration of test material was asymptomatically tolerated. The development of the body weights were unaffected by the intake of the test article. The feed intake was normal. No treatment related blood chemistry changes were seen; especially, no reduction of plasma cholinesterase occurred. There were significant findings at necropsy.
Conclusion Remarks	This study demonstrates a NOAEL in dogs of 200 mg/kg bwlday.
Data Qualities Reliabilities	Reliability code1. Reliable without restrictions.
References	Givaudan-Roure (1990f) A complementary oral toxicity study with *p*-t-butyl alpha-methylhydrocinnamic aldehyde on female dogs during a period of 13 weeks. Unpublished Report to RIFM

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6

Method/guideline	Test material was administered orally for 9 weeks to 2 beagle dogs by means of gelatine capsules. Six dogs were kept as controls and received the empty gelatine capsules.
GLP	NG
Year	1990
Species/Strain	Beagle dogs
Sex	Male
Route of administration	Oral
Doses/concentration	50 ul/kg bw/day for days 1-7, 100 ul/kg bwlday for days 814, 200 ul/kg bwlday for days 15-21, 400 ul/kg bw/day for days 22-50, 600 ul/kg bwlday for days 50-64.
Exposure	64 days
Frequency of treatment	Daily
Control Group and treatment	None
Post exposure observation period	None
Remarks for Test Conditions	Clinical signs and body weights were recorded daily and hematological examinations and clinical chemistry determinations were performed weekly. Histopathology of brain, spinal cord, sciatic nerve, ulnar nerve, liver, kidney, and testes were performed at week 9.
NOAEL (NOEL)	400 ul/kg/day
LOAEL (LOEL)	None
Actual dose received by dose level and sex	Dose of 400 ul/kg/day administered from days 22-50 of the study.
Toxic response/effects by dose level	None
Statistical evaluations	NG
Remarks for Results	One dog showed increased GPT from week 7 onward and increased GLDH from week 4 onward. Mild changes in the seminiferous epithelium of both dogs were not significantly different from that seen in untreated dogs.
Conclusion Remarks	Pilot study that did not establish evidence of testicular effects in dogs.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	Givaudan Corporation (1990e) Pilot study on male dogs with *p*-t-butyl-alpha-methylhydrocinnamic aldehyde following oral administration (increasing dosage) during 9 weeks. Unpublished report to RIFM.

Substance Name	Cinnamaldehyde

CAS No.	104-55-2
Method/guideline	Weanling Osborn-Mendel rats were fed diet containing 1000, 2500, or 10,000 ppm of the test substance for 16 weeks.
GLP	Pre GLP
Year	1967
Species/Strain	Osborne-Mendel rats
Sex	Male and Female
Doses/concentration	1000, 2500 and 10,000 ppm
Exposure	16 weeks
Frequency of treatment	Daily in the diet
Control Group and treatment	Diet containing corn oil
Post exposure observation period	NG
NOAEL (NOEL)	2500 ppm
Actual dose received by dose level and sex	NA
Statistical evaluations	NG
Remarks for Results	No effects were seen at 1000 or 2500 ppm. At 10,000 ppm, slight hepatic cell swelling and slight hyperkeratosis of squamous portion of stomach was noted.
Conclusion Remarks	NOAEL for cinnamaldehyde was shown to be 2500 ppm in rat by oral route.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	This study was published in a peer-reviewed journal.
References	Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.A., and Brouwer, J.B. (1967). Food Flavourings and Compounds of Related Structure. II. Subacute and Chronic Toxicity. Fd. Cosmet. Toxicol. 5: 141-157.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	10 rats were fed a diet containing cinnamaldehyde (est. daily intake 50, 100 & 200 mg/kg) for 12 wks. Physical appearance, behavior and efficiency of food utilization were calculated.
GLP	Pre GLP
Year	**1958**
Species/Strain	Rats

Sex	Male and Female
Route of administration	In diet
Doses/concentration	Estimated daily intake: 50, 100 or 200 mg/kg
Exposure	12 weeks
Frequency of treatment	Daily
Control Group and treatment	Yes
Post exposure observation period	NG
Remarks	After 12 days of treatment, urine of 3 male and 3 female rats were examined for sugar and albumin and blood hemoglobin levels were also determined.
NOAEL (NOEL)	200 mg/kg
Actual dose received by dose level and sex	NA
Toxic response/effects by dose level	None
Statistical evaluations	NG
Remarks for Results	No statistically significantly differences were observed between treated and control groups. No adverse effects were observed on growth, food intake, efficiency of food utilization or other physiological criteria.
Conclusion Remarks	NOAEL was determined to be 200 mg/kg.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
General Remarks	This is a follow-up study for Trubek Laboratories 1958a.
References	Trubek Laboratories (1958b). Toxicological Examination of Cinnamic Aldehyde (Class IV, Part 2).

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Rats were fed test ration containing Cinnamic aldehyde (897ppm), methyl cinnamate (25ppm), ethyl cinnamate (25ppm), cinnamyl cinnamate (25ppm) and alpha methyl cinnamic aldehyde (25ppm) for 12 weeks. Autopsies were performed on all rats.
GLP	Pre GLP
Year	1958
Species/Strain	Rat
Sex	Male and Female
Route of administration	Diet

Doses/concentration	Cinnamic aldehyde (897ppm), methyl cinnamate (25ppm), ethyl cinnamate (25ppm), cinnamyl cinnamate (25ppm) and *alpha* methyl cinnamic aldehyde (25ppm)
Exposure	12 weeks
Frequency of treatment	Continuously in diet
Control Group and treatment	Yes
Post exposure observation period	NG
Remarks	After 12 weeks of treatment, urine from 3 males and 3 females were examined for presence of sugar and albumin and blood hemoglobin levels. Autopsies were performed on all rats. Body weights and organ weight were recorded.
Actual dose received by dose level and sex	NG
Toxic response/effects by dose level	Growth of male rats was retarded but not statistically significant at p=0.05. Food intake **was not** adversely affected. Food intake was not adversely affected. Efficiency of food utilization for both sexes was significantly depressed (male p=0.01& female p=0.05). Urine was free of sugar and albumin. Blood hemoglobin was normal.
Statistical evaluations	NG
Conclusion Remarks	The cinnamate mixture was shown to depress the efficiency of food utilization in both sexes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
General Remarks	See Trubek 1958b for a follow-up study.
References	Trubek (1958a). Toxicological Screening of Components of Food Flavors. Class IV. Cinnamates

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	10 l-86-0
Method/guideline	Test material was applied percutaneously to the shaved dorsa of IO male Sprague-Dawley rats at dose levels of 0.125, 0.25, 0.50 & 1 .00 g/kg/day for 90 consecutive days,
GLP	GLP
Year	1980
Species/Strain	Sprague-Dawley rats
Sex	Male and Female
Route of administration	Percutaneous
Doses|concentration	0.125, 0.25, 0.50 & 1.00 glkglday
Exposure	90 days
Frequency of treatment	Daily

Control Group and treatment	Yes
Remarks	Parameter monitored: Body wt., Food consumption, Hematology, Ophthalmological examination, Blood chemistry (BUN), serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, total bilirubin, fasting serum glucose, serum alkaline phosphatase), urinalysis, Gross Pathology, Histopathology.
LOAEL (LOEL)	0.125 glkglday
Toxic response/effects by dose level	Dose-dependent dermal irritation characterized by erythema, cracking, dryness & sloughing; 5 male & 3 female from 1.0 g/kg died before 90 days; increased food consumption in females @ 0.25, 0.50, & 1 .00 g/kg; inconsistent changes in hemoglobin, hematocrit, erythrocyte count, SGOT & SGPT; consistent elevation in white blood cell and the segmented neutrophil counts @ 0.50 & 1 .00 g/kg; reduced lymphocyte count in males @ 1.00 g/kg; elevated white blood cell count in females @ 0.25-1.00 g/kg; reduced serum glucose & increased BUN & SAP in all rats; dosedependent irritation of the GI-tract and the treated skin; increased liver & kidney wt in female @ 0.25-I .00 g/kg; at 1 .00 g/kg: hepatic hydropic vacuolization & single cell degeneration, splenic lymphoid depletion & fibrosis, focal gastric ulceration & chronic necrotizing dermatitis with acanthosis, hyperkeratosis & sebaceous gland hyperplasia; dose-dependent increases in the myeloid-erythroid & decreases of the cell-fat ratios.
Conclusion Remarks	Percutaneous administration of Hexyl Cinnamic Aldehyde for 90 days produced multisystemic toxicity in the rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	Lough, R., Owston, E., Klein, G., Qureshi, S., and Bier, C. (1980). A subacute (90 Day) Percutaeous Toxicity Study of Hexyl Cinnamic Aldehyde in the Albino Rat. Unpublished. Bio-Research Lab. Report to RIFM.

Substance Name	Cinnamalydehyde
CAS No.	104-55-2
Method/guideline	Subchronic study. 10 mg of test substance was given every other day in normal or low protein diet (9% casein). Duration not given.
GLP	**No**
Year	1965
Species/Strain	Not reported
Sex	Not reported
Route of administration	Diet

Doses/concentration	10 or 50 mg every other day
Exposure	Not reported
Frequency of treatment	Every other day
Control Group and treatment	Not reported
Post exposure observation period	NG
Remarks	Article in Romanian. No details given in the English Abstract.
LOAEL (LOEL)	10 mg
Actual dose received by dose level and sex	NG
Toxic response/effects by dose level	The activity of liver aldolase showed significant increase and the activity of succindehydrogenase showed a tendency to decrease.
Statistical evaluations	NG
Remarks for Results	No effect on weight gain, food ingestion and protein efficiency. No effect on the liver weight and ascorbic acid content and the aspartic glutamic transaminase activity
Conclusion Remarks	Administration of test substance (10 mg) resulted in increased activity of liver aldolase and the activity of succindehydrogenase showed a tendency to decrease.
Data Qualities Reliabilities	Reliability code. 3. Data not reliable.
Remarks for Data Reliability	Article in Romanian. No details given in the English Abstract.
References	Sporn A. (1965). Investigation of the Toxicity of Cynamic Aldehyde. Igiena 14(6): 339-346.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Two male rhesus monkeys (Macaca Mulatta) were orally administered with 100 mglkglday of test substance suspended in fluid-baby food for 5 consecutive days.
GLP	**NG**
Year	**1990**
Species/Strain	Rhesus monkey Macaca Mulatta
Sex	Male
Route of administration	Oral in food
Doses/concentration	100 mglkglday for 5 consecutive days.
Exposure	5 days
Frequency of treatment	Daily

Remarks	At the end of the study, the Rhesus monkey were anesthetized and perfused with glutaraldehyde. Testes and epididymies were microscopically examined.
NOAEL (NOEL)	100 mg/kg
Toxic response/effects by dose level	None
Remarks for Results	No changes in body weight or testes were noted.
Conclusion Remarks	No toxic effects were observed in monkeys treated with 100 mglkg for 5 days.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Givaudan Roure (1990g). A 5-day oral toxicity study with *p*-t-butyl-alpha-methylhydrocinnamic aldehyde in male rhesus monkeys. Unpublished, Report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	The test material was dermally administered to male albino rats at dose levels of 250, 500, 1000 & 2000 mglkglday for 5 days.
GLP	NG
Year	1991
Species/Strain	Albino rats
Sex	Male
Route of administration	Dermal
Doses/concentration	250, 500, 1000 and 2000 mg/kg/day for 5 days.
Exposure	5 days
Frequency of treatment	Daily
Remarks	The mortalities, adverse symptoms & lower body weights were recorded. At termination, all rats were euthanized and subjected to a full necropsy. Testes and epididymides were microscopically examined.
NOAEL (NOEL)	1000 mglkglday
LOAEL (LOEL)	2000 mglkglday
Toxic response/effects by dose level	No chemical related mortalities, Initial disturbance of body weight at 2000 mg/kg. No compound related gross lesions; Atrophy in the testes at 2000 mglkglday.
Conclusion Remarks	Treatment of fat with 2000 mg/g/day for 5 days dermally resulted in disturbance in body weight and atrophy in the testes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Givaudan Roure (1991). A 5-day toxicity study with *p*-t-butyl-alpha-methy-hydrocinnamic aldehyde on male rats: dermal administration compared to oral administration. Unpublished.

Report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	The test material was orally administered to male albino rats at dose levels of 25, 50 and 100 mglkglday for 5 days.
GLP	N G
Year	1991
Sex	Male
Route of administration	Oral
Doses/concentration	25, 50 and 100 mglkglday for 5 days.
Exposure	5 days
Frequency of treatment	Daily
Remarks	The mortalities, general symptoms & body weights were recorded. At termination, all rats were euthanized and subjected to a full necropsy. Testes and epididymides were microscopically examined.
NOAEL (NOEL)	25 mglkglday
LOAEL (LOEL)	50 mglkglday
Toxic response/effects by dose level	No chemical related mortalities, Initial disturbance of body weight at 50 and 100 mg/kg. No compound related gross lesions; Atrophy in the testes at 50 and 100 mg/kg/day.
Conclusion Remarks	Treatment of rat with 50 or 100 mg/g/day for 5 days orally resulted in disturbance in body weight and atrophy in the testes,
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Givaudan Roure (1991). A 5-day toxicity study with *p*-t-butyl-alpha-methy-hydrocinnamic aldehyde on male rats: dermal administration compared to oral administration. Unpublished. Report to RIFM.

Substance Name	alpha-Amylcinnamaldehyde (at least 97% pure), pale yellow liquid with a floral odor.
CAS No.	122-40-7
Method/guideline	15 Male & 15 female rats were fed diet containing the test substance for 14 weeks at dietary levels of 0, 80, 400 or 4000 ppm. Rats were killed by exanguination under barbiturate anesthesia. Parameters monitored were: body wt, hemoglobin content see below.
GLP	N G
Year	1973

Species/Strain	Rats CFE strain
Sex	Male and Female
Route of administration	Oral
Doses/concentration	0, 80, 400 or 4000 ppm
Exposure	14 weeks
Frequency of treatment	Continuous
Control Group and treatment	Diet without the test material
Remarks	Parameters measured: packed cell volume, counts of erythrocytes, total leucocytes & individual types of lecocytes, serum, urea, glucose, total protein, albumin, activation of glutamic oxaloacetate & glutamic-pyruvic transaminase & lactic dehydrogenase, urinalysis for the final week of treatment. Each animal was given an autopsy.
NOAEL (NOEL)	400 ppm
LOAEL (LOEL)	4000 ppm
Actual dose received by dose level and sex	Male: 6.1, 29.9 or 287.3 mglkglday; female:6.7, 34.9 or 320.3 mglkglday
Toxic response/effects by dose level	Increase in the relative liver & kidney weights of the rats fed diet containing 4000 ppm of the test substance for 14 weeks. These were not associated with any histopathological changes.
Remarks for Results	No differences over controls were seen in the rate of body wt gain, the consumption of food & water, hematological measurements, serum analyses, urinary cell excretion or renal concentration tests.
Conclusion Remarks	NOAEL for the test material was shown to be 400 ppm.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Carpanini, F.M.B., Gaunt, I.F., Wright, M.G., Grasso, P. and Gangolli, SD. (1973), Short-Term Toxicity of Amyl Cinnamic Aldehyde in Rats. Fd. Cosmet. Toxicol. 11: 725-734.

Substance Name	Cinnamaldehyde (98% pure)
CAS No.	104-55-2
Method/guideline	Rats were administered the test substance by gavage for 2 wks.
GLP	**NG**
Year	1994
Species/Strain	F344/N rats
Sex	Male and Female

Route of administration	Gavage
Doses/concentration	0, 235, 470, 940, 1880 & 3750 mglkglday for 14 days
Exposure	14 days
Frequency of treatment	Daily
Control Group and treatment	Corn oil gavage
Remarks	A complete autopsy was performed on all animals that died, and at the termination of the study on all treated and control animals. Body wt and the organ wt. of the liver, right kidney and the spleen were determined.
NOAEL (NOEL)	235 mglkglday
LOAEL (LOEL)	470 mglkglday
Toxic response/effects by dose level	All rats dosed at 1880 & 3750 mglkglday died or were killed when moribund during the first 7 days of dosing. Microscopic lesions included a minimal to moderate forestomach hyperplasia in males at doses of 470 mglkglday and higher.
Statistical evaluations	ANOVA
Remarks for Results	There were no consistent differences in organ w-t or organ wt: body wt ratios between surviving treated or controls. Clinical signs and gross lesions were absent in surviving rats,
Conclusion Remarks	Test substance at dose 470 mglkglday and above produces forestomach hyperplasia and was lethal at dose of 1880 and above.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Herbert, C. D., Yuan, J. and Dieter, M.P. (1994). Comparison of the Toxicity of Cinnamaldehyde When Administered by Microencapsulation in Feed or by Corn Oil Gavage. Food and Chemical Toxicology 32(12): 1107-I 115.

Substance Name	Cinnamaldehyde (98% pure)
CAS No.	104-55-2
Method/guideline	Mice were administered the test substance by gavage for 3 weeks.
GLP	**NG**
Year	1994
Species/Strain	B6C3F1 mice
Sex	Male and Female
Route of administration	Gavage
Doses/concentration	656, 1310, 2620, 5250 & 10500 mglkglday

Exposure	21 days
Frequency of treatment	Daily
Control Group and treatment	Corn-oil gavage
Remarks	A complete autopsy was performed on all animals that died, and at the termination of the study on all treated and control animals. Body wt and the organ wt. of the liver, right kidney and the spleen were determined.
NOAEL (NOEL)	656 mglkglday
LOAEL (LOEL)	1310 mg/kg/day
Toxic response/effects by dose level	All mice gavaged at doses of 5250 and 10,500 mg/kg/day, as well as all female mice and three male mice dosed with 2620 mglkglday died within first 2 days. No clinical signs, or gross or microscopic lesions were visible in these mice. The only microscopic lesions observed in surviving mice were a minimal to mild forestomach hyperplasia & a minimal kidney nephropathy at doses of 1310 mg/kg/day and higher.
Statistical evaluations	ANOVA
Conclusion Remarks	Test substance at doses 1310 mglkglday and above produce forestomach hyperplasia and was lethal at dose of 5250 and above.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Herbert, C. D., Yuan, J. and Dieter, M.P. (1994). Comparison of the Toxicity of Cinnamaldehyde When Administered by Microencapsulation in Feed or by Corn Oil Gavage. Food and Chemical Toxicology 32(12): 1107-I 115.

Substance Name	Cinnamaldehyde (98% pure)
CAS No.	104-55-2
Methodlguideline	A group of rats were fed a diet containing 0, 0.625, 1.25, 2.5, 5.0 or 10% Cinnamaldehyde microcapsules for 14 days.
GLP	**NG**
Year	**1994**
Species/Strain	F344/N rats
Sex	Male and Female
Route of administration	Oral in diet
Doses/concentration	A group of rats were fed a diet containing 0, 0.625, 1.25, 2.5, 5.0 or 10% Cinnamaldehyde microcapsules for 14 days.
Exposure	14 days
Frequency of treatment	Continuous

Remarks	A complete autopsy was performed on all animals that died, and at the termination of the study on all treated and control animals. Body wt and the organ wt. of the liver, right kidney and the spleen were determined.
NOAEL (NOEL)	0.625%
LOAEL (LOEL)	1.25%
Toxic response/effects by dose level	Marked doserelated depression in body wt gain, slight decrease in spleen: body wt ratio for male rats in 10% group, dose dependent decrease in food consumption. Gross lesions in both sexes were limited to a reduction in the size of reproductive organs and secondary sex glands (seminal vesicles & prostates of males & ovaries & uteri of females). Hyperplasia of the forestomach
Statistical evaluations	ANOVA
Conclusion Remarks	Treatment of rat with microencapsulated cinnamaldehyde resulted in marked dose-dependent depression of body weight, hypoplastic changes in reproductive organs & accessory sex glands and hyperplasia of the forestomach mucosa.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Herbert, C. D., Yuan, J. and Dieter, M.P. (1994). Comparison of the Toxicity of Cinnamaldehyde When Administered by Microencapsulation in Feed or by Corn Oil Gavage. Food and Chemical Toxicology 32(12): 1107-I 115.

Substance Name	Cinnamaldehyde (98% pure)
CAS No.	104-55-2
Method/guideline	A group of rats were fed a diet containing 0, 0.625, 1.25, 2.5, 5.0 or 10% Cinnamaldehyde microcapsules for 21 days.
GLP	**NG**
Year	**1994**
Species/Strain	B6C3F1 mice
Sex	Male and Female
Route of administration	Oral in feed
Doses/concentration	A group of mice were fed a diet containing 0, 0.625, 1.25, 2.5, 5.0 or 10% Cinnamaldehyde microcapsules for 21 days.
Exposure	21 days
Frequency of treatment	Continuous
Remarks	A complete autopsy was performed on all animals that died, and at the termination of the study on all treated and control animals. Body wt and the organ wt. of the liver, right kidney and the spleen were determined.

NOAEL (NOEL)	1.25%
LOAEL (LOEL)	2.5%
Toxic response/effects by dose level	Dose-related decrease in body wt, decrease in absolute liver and kidney wt., hyperplasia of the forestomach epithelium at highest dose (10%) characterized by a focal thickening of the stratified squamous epithelium, accompanied by hyperkeratosis.
Statistical evaluations	ANOVA
Conclusion Remarks	Treatment of mice with microencapsulated cinnamaldehyde resulted in dose-dependent depression of body weight and hyperplasia of the forestomach epithelium at highest dose (10%) characterized by a focal thickening of the stratified squamous epithelium, accompanied by hyperkeratosis.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions,
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Herbert, C. D., Yuan, J. and Dieter, M.P. (1994). Comparison of the Toxicity of Cinnamaldehyde When Administered by Microencapsulation in Feed or by Corn Oil Gavage. Food and Chemical Toxicology 32(12): 1107-I 1 15.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	90-day subchronic dermal toxicity study.
GLP	N G
Year	1981
Species/Strain	Sprague-Dawley Rats
Sex	Male and Female
Route of administration	Dermal
Doses/concentration	25 mg/kg
Exposure	90 days
Frequency of treatment	Daily
Control Group and treatment	Phenyl ethyl alcohol
Remarks	5% of the test substance in phenyl ethyl alcohol at a dose of 25 mg/kg was applied topically to the clipped backs of Sprague-Dawley rats (5 male and 5 female). A control group of 5 male and 5 female rats received phenyl ethyl alcohol (1 ml/kg). Body wt, hematology, clinical chemistry & urinalysis parameters were evaluated. All animals were examined grossly & liver & kidneys were weighed. Microscopic examination of the skin, liver, kidney & spinal cord was conducted.

NOAEL (NOEL)	25 mglkg
Toxic response/effects by dose level	None
Remarks for Results	One male rat died on day 14 with an evidence of a lung infection. The death was not considered to be related to treatment.
Conclusion Remarks	There was no evidence of toxicity induced by treatment with the test articles.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
References	Moreno (1981a). 90 Day subacute dermal toxicity in rats with hexyl cinnamic aldehyde, gamma-methyl ionone and phenyl ethyl alcohol. Report to RIFM. Unpublished.

Substance Name	p-t-Butyl-alpha-methylhydrocinnamaldehyde (97.8% pure), liquid, colorless to pale yellowish.
CAS No.	80-54-6
Method/guideline	Subchronic toxicity study. Test substance was administered to albino rats by oral gavage. Six test groups consisting of 14 rats per sex were dosed at 2, 5, 25 & 50 mg/kg once daily, 5 days/wk for 13 weeks.
GLP	Yes
Year	1990
Species/Strain	Rats, outbred
Sex	Male and Female
Route of administration	Oral gavage
Doses/concentration	0, 2, 5, 25 & 50 mglkglday,
Exposure	90 days
Frequency of treatment	5 days per week for 13 weeks
Control Group and treatment	Rape oil 1 ml/kg
Post exposure observation period	4 weeks
Remarks	A satellite group was treated with 50 mglkg and was observed during a post-treatment period of 4 weeks. Mortalities, general symptoms & body weights were recorded. Hematology & biochemistry determinations were performed. All rats were autopsied. Organs & tissues of the control rats & the rats treated w/50 mg/kg as well as liver of all rats, the testes & epididymides of all male rats & the adrenal glands of all female rats were microscopically examined.
NOAEL (NOEL)	5.0 mg/kg
LOAEL (LOEL)	25 mglkg
Toxic response/effects by dose level	Treatment related histopathology findings were spermatoceles & testicular atrophy in male rats treated with 50 mg/kg

Statistical evaluations	Dunn-test, Jonck-heere-test, U-test
Remarks for Results	Deaths related to treatment did not occur throughout the test and follow-up period. Loss of hair was seen in female rats treated with 50 mg/kg. The body wt development of tats of all test groups took a normal course throughout the test and follow-up period. The treatment did not change hematological parameters. In male and female rats treated with 25 and 50 mg/kg, the plasma cholinesterase was reversibly decreased and the plasma cholesterol levels were lower than in control rats
Conclusion Remarks	Treatment with test material resulted in spermatoceles and testicular atrophy in male rats at the dose of 50 mg/kg. Also, a decrease in the plasma cholinesterase activity and plasma cholesterol was seen in rats treated with the test material at the dose of 25 mg/kg and above.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	The study was conducted in accordance with EPA Guidelines, OECD Guidelines and Swiss Guidelines.
References	Givaudan-Roure (1990d) A supplementary study with *p*-t-butyl-alpha-methylhydrocinnamic aldehyde on rats for determining acetylcholinesterase and cholinesterase activity of blood plasma, erythrocytes, liver and brain tissue. Unpublished Report to RIFM.

Substance Name	p-t-Butyl-alpha-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	Groups of 8 male rats were treated with 25, 50, 100, 200 & 400 mglkglday of the test substance orally for 5 consecutive days.
GLP	Likely
Year	1990
Species/Strain	Rats
Sex	Male
Route of administration	Oral (gavage)
Doses/concentration	0, 25, 50, 100, 200 & 400 mglkglday
Exposure	5 consecutive days
Frequency of treatment	Daily
Control Group and treatment	Yes
Remarks	This is a follow-up study on the previous study by the same group with similar results
Toxic response/effects by dose level	Disturbed the spermatogenesis and spermiogenesis @ 100 mg/kg & above, morphological alterations in the seminiferous epithelium preceded the formation of detectable spermatoceles.
Remarks for Results	No deaths reported, other observations reported: shaggy fur, hunched posture, hematuria, paresis of the forelegs, initial

	hunched posture, hematuria, paresis of the forelegs, initial disturbance of weight development @ 50, 100 & 200 mg/kg/day which recovered on day 4; continued loss of body weight @ 400 mg/kg; At autopsy, delineation of hepatic lobules, small prostate and seminal vesicles, and reddened testes were seen. Testes weight was decreased in rats treated with 100 mg/kg and above, histological examination of the testes revealed injuries of seminiferous epithelium that means degeneration and loss of germ cells in rats treated with 50 mg/kg and above.
Conclusion Remarks	Administration of the test substance for 5 consecutive days resulted in disturbance of the spermatogenesis and spermiogenesis. The, morphological alterations in the seminiferous epithelium preceded the formation of detectable spermatoceles.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Two of the four control rats displayed a disturbance of spermiogenesis with desquamation of young spermatids. Also, authors states that rat seems to be much more prone to spermatoceles than e.g. the mouse, therefore the rat might be a bad model for detecting epididymal side effects of chemicals. Authors also claim that the rat was found to be only species to suffer from adverse testicular and epididymal effect from exposure to the test chemical.
References	Givaudan Roure (199Oc). Re-evaluation of testicular and epididymal side effects caused by p-t-butyl alpha-methyldihydrocinnamic aldehyde in rats following short (5 days) and subchronic (13 weeks) oral administration. Unpublished. Report to RIFM.

Substance Name	*p*-t-Butyl-*alpha*-methyldihydrocinnamaldehyde
CAS No.	80-54-6
Method/guideline	13-weeks Subchronic study. Groups of 14 male and 14 female rats were treated by oral gavage with 0, 5, 25, and 50 mg/kg for five days per week for 13 consecutive weeks.
GLP	Likely
Year	**1990**
Species/Strain	Rat
Sex	Male
Route of administration	Oral (gavage)
Doses/concentration	0, 2, 5, 25 and 50 mg/kg/day
Exposure	13 weeks
Frequency of treatment	5 days per week for 13 weeks
Control Group and treatment	**Yes**

Post exposure observation period	**4 weeks**
Remarks	The rats were sacrificed with exception of 4 control rats per sex and a satellite group of 14 rats per sex treated with 50 mg/kg. These rats were necropsied after a treatment-free period of approximately 4 weeks.
NOAEL (NOEL)	5 mg/kg/day
LOAEL (LOEL)	25 mglkglday
Toxic response/effects by dose level	Necropsy findings comprised spermatoceles and the occurrence of small testes in male rats treated with 50 mg/kg. Treatment-related histopathology findings were spermatoceles and testicular atrophy in male rats treated with 50 mg/kg.
Remarks for Results	No treatment related deaths, Other treatment related observation included: Loss of hair in female rats, reversible decrease in cholinesterase activity and the plasma cholesterol levels in male and female rats, Absolute and relative weights were elevated in male and female rats treated with 25 and 50 mg/kg. The absolute and relative weights of adrenal glands were elevated in female rats treated with 25 and 50 mg/kg.
Conclusion Remarks	Administration of the test substance for 5 consecutive days resulted in disturbance of the spermatogenesis and spermiogenesis. The morphological alterations in the seminiferous epithelium preceded the formation of detectable spermatoceles.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Two of the four control rats displayed a disturbance of spermiogenesis with desquamation of young spermatids. Also, authors states that rat seems to be much more prone to spermatoceles than e.g. the mouse, therefore the rat might be a bad model for detecting epididymal side effects of chemicals. Authors also claim that the rat was found to be only species to suffer from adverse testicular and epididymal effect from exposure to the test chemical.
References	Givaudan Roure (199Oc). Re-evaluation of testicular and epididymal side effects caused by p-t-butyl *alpha*-methylhydrocinnamic aldehyde in rats following short (5 days) and subchronic (13 weeks) oral administration. Unpublished. Report to RIFM.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Test substance was administered orally to white rats for 25 day.
GLP	**NG**
Year	**1974**
Species/Strain	White rat
Sex	Male

Route of administration	Oral (gavage)
Doses/concentration	0.02 LD50 (LD50 = 3400 mg/kg)
Exposure	25days
Control Group and treatment	Sunflower seed oil
Remarks	Following parameters were monitored: Plasma Cholinesterase activity, serum aldolases activity, sorbitol dehydrogenase, aspartate and alanine aminotransferase, content of SH groups, total protein level in the blood serum.
Toxic response/effects by dose level	No effects were reported.
Conclusion Remarks	No adverse effects were seen in the rats treated with cinnamaldehyde for 25 days at a dose of 0.02LD50.
Data Qualities Reliabilities	Reliability code 3. Data not reliable.
Remarks for Data Reliability	Original article in Russian. Very few details given.
References	Zaitsev, A.N. and Rakhmanina, N.L. (1974). Some Data on the Toxic Properties of Phenylethyl and Cinnamyl Alcohols. Vopr Pitaniya 6: 48-53.

Substance Name	alpha-Hexylcinnamaldehyde
CAS No.	101-86-O
Method/guideline	Test material was applied percutaneously to the shaved dorsa of 10 male Sprague-Dawley rats at dose levels of 0.15, 0.375, 0.75, 1.5 and 3.0 glkglday for 28 consecutive days,
GLP	Yes
Year	1980
Species/Strain	Sprague-Dawley rats
Sex	Male
Route of administration	Percutaneous
Doses/concentration	0.15, 0.375, 0.75, 1.5 and 3.0 glkglday
Exposure	28 days
Frequency of treatment	Daily
Control Group and treatment	None
Post exposure observation period	None
Remarks	Parameter monitored: body wt., food consumption, hematology, blood chemistry (BUN), serum glutamic pyruvic transaminase, serum glutanic oxalacetic transaminase, total bilirubin, fasting serum glucose, serum alkaline phosphatase), gross pathology, histopathology.

LOAEL (LOEL)	0.15 g/kg/kg
Toxic response/effects by dose level	Erythema and eschar formation with cracking and dryness @all doses, hyperirritability @ all doses except 0.375 g/kg/day, reduced body wt @ 1.5 & 3.0 g/kg/day, depressed food intake @ 3.0 g/kg/day, dose-related negative effect on clotting time & white blood cell count, shift in the proportion of segmented neutrophils to lymphocytes @ 1.5 & 3.0 g/kg, increase in BUN, SAP, SGPT, SGOT & decrease in Glucose, thickening of the skin & erythema of dermis & epidermis, body emaciation, congested lungs, GI irritation, decrease in absolute & relative thymus & spleen, dermatitis with mild to severe hyperkeratosis at all doses except 0.15 g/kg, focal dilation of tubules in kidney @ 0.75 & 1.5 g/kg, sub-acute to chronic necrotizing & hemorragic enteritis
Statistical evaluations	No statistical evaluation was done.
Remarks for Results	Because small number of animals (2 per group) no statistical evaluation was done.
Conclusion Remarks	Repeated percutaneous administration of alpha hexylcinnamic aldehyde resulted in changes in gross pathology, histopathology, clinical and biochemical chemistry and hematological parameters.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was conducted in accordance with GLP.
References	Lough, R., Owston, E., Bier, C., and Qureshi, S. (1980). A Range finding evaluation of the toxicity of Hexyl Cinnamic aldehyde Administered percutaneously in the rat. Unpublished. Bio-Research Laboratories Ltd. Report to RIFM.

Substance Name	alpha-Amylcinnamaldehyde
CAS No.	**122-40-7**
Method/guideline	15 Male & 15 Female rats of the FDRL strains were fed diet containing 2% test substance diluted in cotton-seed oil for 12 weeks. At 90 days, autopsy was performed. Hematological and blood chemical determinations were also made.
GLP	Pre GLP
Year	**1965**
Species/Strain	FDRL Strain Rats
Sex	Male and Female
Route of administration	Feed
Doses/concentration	**2%** in feed
Exposure	12 weeks
Frequency of treatment	Feed diet with test material for 12 weeks

Control Group and treatment	Feed without tests material
Post exposure observation period	**NG**
NOAEL (NOEL)	2 %
Statistical evaluations	**NG**
Remarks for Results	No treatment related adverse effects were noted in the parameters measured.
Conclusion Remarks	This study demonstrates a NOAEL in rats was shown to be 2% in feed.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Oser, B.L., Carson, S, and Oser, M. (1965) Toxicological Tests on Flavouring Matters. Fd. Cosmet. Toxicol. 3: 563-569.

4.5 Reproductive Toxicity

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	**NG**
Test Type	Two generations
GLP	**NG**
Year	**1965**
Species/Strain	Not given
Sex	Female
Route of administration	Unreported
Duration of test	223 & 210 days
Doses/concentration	2 mg cinnamaldehyde every other day
Premating Exposure period for males	NA
Frequency of treatment	Continuous
Control Group and treatment	Not mentioned
Remarks for Test Conditions	Article in Romanian. English abstract contains very few details. Parameters monitored: body weight, reproduction ability (no. of pregnant females, no.& weight of the young one at birth), the development & viability of the young animals, the protein & lipid contents of liver & liver activity.

Remarks for Results	Treatment resulted in significant ($p<0.01$) 20-22% increase in the lipid content of the liver as compared to control groups. The other indicators were not affected. No details were given whether the observed effect was in offspring or Parents. Article in Romanian.
Conclusion Remarks	Administration of the test substance caused in increase in liver lipid content in the unspecified group.
Data Qualities Reliabilities	Reliability code 3. Data not reliable.
Remarks for Data Reliability	Article in Romanian. The English abstract contains very few details.
General Remarks	Article is in Romanian. Need English translation of more details,
References	Sporn A. (1965). Investigation of the Toxicity of Cynamic Aldehyd. Igiena 14(6): 339346.

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	Cinnamic aldehyde was administered by gavage to Sprague-Dawley rats on days 7-17 of pregnancy at doses of 5, 25 or 250 mglkglday.
Test Type	Pre-Natal (Segment II) Toxicity Study.
GLP	NG
Year	1989
Species/Strain	Sprague-Dawley rats
Sex	Female
Route of administration	Gavage
Duration of test	Days 7-17 of pregnancy
Doses/concentration	0, 5, 25 or 250 mg/kg/day
Premating Exposure period for males	None
Premating Exposure period for females	None
Frequency of treatment	Daily
Control Group and treatment	Vehicle (olive oil)
NOAEL (NOEL)	None
LOAEL (LOEL)	5 mg/kg/day
Actual dose received by dose level and sex	0, 5, 25 or 250 mglkglday
Parental data and F1	No signs of maternal toxicity, decreased weight gain between day 7 & 20 with decrease in food intake.
Offspring toxicity Fl and F2	Increased incidence of poor cranial ossification, decreased ossification of tympanic bulla at 25 or 250 mg/kg/day, increased

	incidence of dilated pelvis/reduced papilla in kidney, increased incidence of reduced cranial ossification, dilated ureter. One case of facial malformation & few cases of hypoplastic/dysplastic kidney.
Statistical evaluations	Kruskal-Walks test, Mann-Wittney test
Remarks for Results	Authors abstract state "significant increases of the incidences of dilated pelvis/reduced papilla in the kidney, dilated ureters>2 abnormal sternebrae per fetus were detected in the 2-mg/kg group." However no such dose group (2-mg/kg) is reported in either the methodology or the Results section.
Conclusion Remarks	Administration of Cinnamaldehyde to pregnant rats resulted in increased incidence of poor cranial ossification and reduced ossification of the tympanic bulla. Significant increases of the incidences of dilated pelvis/reduced papilla in the kidney, ureters > 2 abnormal sternebrae per fetus were also reported.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-review journal.
General Remarks	The changes in treated groups might have been influenced by the greater litter size in the higher dose groups (There was significantly higher pre-implantation loss in control as compared to the treated groups).
References	Mantovani, A., Stazi, A.V., Macri, C., Ricciardi, C., Piccioni, A. and Badellino, W. (1989). Pre-Natal (Segment II) Toxicity Study of Cinnamic Aldehyde in the Sprague-Dawley Rats.Food and Chemical Toxicology 27(12): 781-786.

Substance Name	Instead of Cinnamaldehyde, structurally related chemicals, Cinnamic alcohol and cinnamic acid were used in this study
CAS No.	104-55-2
Method/guideline	The chemicals were studied at doses of 0.02 and 0.002 LD50 value; 53.5 mg/kg cinnamic alcohol and 50 mg/kg cinnamic acid. The animals were exposed to the test chemical during the entire pregnancy.
Test Type	Reproductive toxicity.
GLP	N G
Year	1975
Species/Strain	Albino rat
Sex	Female
Route of administration	Oral
Duration of test	20 days
Doses/concentration	53.5 mg/kg cinnamic alcohol and 50 mg/kg cinnamic acid
Premating Exposure period for males	None

Premating Exposure period for females	None
Frequency of treatment	Daily
Control Group and treatment	Yes
Remarks for Test Conditions	There were 14-15 female rats in each group. On the 20th day of pregnancy 69 rats from each group were decapitated, the embryos were taken from the uterus and studied. The remaining pregnant rats were left until the natural birth and the development of the progeny was observed during the postnatal period for one month. The parameters monitored: embryonic mortality, number of live embryos, birth weight, length, number of external and internal anomalies in the development of the embryos.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Offspring toxicity F1 and F2	Cinnamic alcohol and cinnamic acid administration perorally to rats during the whole pregnancy is doses of 53.5 and 50 mg/kg caused no embryotoxic effect.
Conclusion Remarks	Cinnamic alcohol and cinnamic acid administration perorally to rats during the whole pregnancy is doses of 53.5 and 50 mg/kg caused no embryotoxic effect.
References	Zaitsev, A. N. and Maganova, N. B. (1975). Embryotoxic Action of Some Food Aromatizers. Voprosy Pitaniya 3: 64--68.

4.6 Developmental Toxicity

Substance Name	Cinnamaldehyde
CAS No.	104-55-2
Method/guideline	The study was conducted in two phases: initial dosefinding study followed by a reproductive phase, which employed a single dose level. In both phases treatment was administered by gavage using a standard dosing volume of 10 ml/kg.
Test Type	Developmental Toxicity Test
GLP	NG
Year	1987
Species/Strain	CD1 mice
Sex	Female
Route of administration	Oral (gavage)
Duration of test	From Gestation Day 6-13
DosesIconcentration	1200 mg/kg/day
Premating Exposure period for males	None

for males	
Premating Exposure period for females	None
Frequency of treatment	Daily
Control Group and treatment	Corn oil
Remarks for Test Conditions	For Phase I, test chemical was tested at five dose levels using ten virgin female mice for 8 consecutive days. For the Reproductive phase, the LD10 predicted on the basis of dose finding results was the single dose used. Treatment in the reproductive phase were administered once daily on Gestation day 6-13
NOAEL (NOEL)	1200 mg/kg/day
Parental data and F1	As compared to controls, no changes were seen in: Number of dead/total; % body weight change and delivery of viable litter.
Offspring toxicity F1 and F2	As compared to control, no changes were seen in: Number of stillborn/litter; %survival; birth weight and weight gain.
Statistical evaluations	Z-tail ANOVA, Z-tail Fischer's exact test,
Conclusion Remarks	Administration of Cinnamaldehyde to pregnant female mice (gestation day 6-13) did not produce any maternal, fetal or neonatal toxicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The study was published in a peer-reviewed journal.
References	Hardin, B.D.m Schufer, R.L., Burg, J. R., Sooth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V. J. and Smith, K.N. (1987). Evaluation of 60 Chemicals in a Preliminary Developmental Toxicity Test. Teratogenesis, Carcinogenesis and Mutagenesis 7: 2948.